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Internal Secretions

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Manuscripts of three types of original work are desired for publication:

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THIS NUMBER AND THE NEXT

In this number will be found the third of the series of papers which have been prepared by Drs. Rowe and Lawrence, of Boston, one of the several very interesting papers presented at the Minneapolis meeting, a valuable paper contributed by Dr. McLean, and three shorter papers whose interest and value are not diminished by the fact that they are shorter.

We have on hand and mostly in type the following papers:

Studies on Oxytocin and Vasopressin: The Effect on Frog Melanophores. L. W. Rowe, M.S., Detroit.

Recent Progress in the Investigation of the Posterior Lobe of the Pituitary Gland. Edwin P. Bugbee, M.D., and Oliver Kamm, M.D., Detroit.

The Thyroid Gland in Infections; the Effect upon the Basal Metabolic Rate. N. A. Womack, W. H. Cole and A. G. Heideman, of St. Louis.

Ovarian and Placental Hormone Effects in Normal, Immature, Albino Rats. George T. Golding and F. T. Ramirez, Columbia, Mo.

Studies of the Endocrine Glands. IV. The Male and Female Gonads. A. W. Rowe and C. H. Lawrence, Boston.

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A Case of Diabetes, Refractory to Insulin, with Hyperplastic and Adenomatous Adrenals. R. A. Moore, Columbus.

The Vaginal Smear Method of Assay of the Ovarian Hormone. Lydia C. Kahnt and Edward A. Doisy, St. Louis.

The Distribution of the Ovarian Hormone between Liquor Folliculi and the Residual Tissue. Sidney Thayer and Edward A. Doisy, St. Louis.

Iodine Deficiency Symptoms and their Significance in Animal Nutrition and Pathology. John M. Evvard, Ames, Iowa.

Pronounced Exophthalmos in a Case of Adenomatous Goiter without Hyperplasia. Dorothy Atkinson, H. Lisser and H. Clare Shepardson, San Francisco.

The Oral Administration of Adrenalin. G. Giragossintz and H. Mackler, Berkeley, Calif.

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Endocrinology

The Bulletin *of the*
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Internal Secretions

July-August, 1928

STUDIES OF THE ENDOCRINE GLANDS
III. THE THYROID

CHARLES HENRY LAWRENCE, M. D.
and
ALLAN WINTER ROWE, Ph. D.
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BOSTON

PART I

In a recent publication (1) the authors have discussed the results obtained from the study of a group of pituitary cases by the application of a general method of diagnosis, the details of which have recently appeared (2). This present communication deals with the findings in a series of cases presenting some phase of thyroid disease as the principal etiological element. As the establishment of criteria of performance and methods of approach have been discussed in detail in the earlier papers, attention may be directed at once to the present thesis.

INTRODUCTION

With the sole exception of the pancreas and its endocrine malfunction producing diabetes, no one of the proven ductless glands has been so thoroughly and successfully studied as has

the thyroid.* The early recognition of the association of the two classic syndromes, exophthalmic goiter and myxedema, with aberrant function of the gland, is a most important factor. Even more important has been the development of an unimpeachable surgical technique for the control of hyperfunction, and equally, the demonstration of the efficacy of preparations of the gland to correct lowered activity by a replacement therapy. The preparation by Kendall (3) of a single substance capable of duplicating in large measure the pharmacologic action of the glandular extract, is the latest step in the development. In advanced Graves' disease, long-standing myxedema, or well-established cretinism, the several pictures presented conform so nearly to the classic type that diagnosis is relatively simple and certain. In incipient or even intermediate stages, however, many cases present which may not be accurately traced to a thyroid malfunction. Further, in a not inappreciable number of individuals, thyroid disease may present a chain of symptoms utterly at variance with the classic types, and these will certainly escape proper diagnosis if only subjective findings are considered. Two pitfalls, grave at least for the patient, must sedulously be avoided. In many metabolic disturbances, end results in the form of symptoms may be suggestive of thyroid malfunction. To confirm these indications by a single test—the basal metabolic rate—and by its sole authority to establish a diagnosis, is an entirely unwarrantable procedure. Several non-endocrine conditions simulate one or another form of thyroid disease and may even exhibit a seemingly characteristic change in the metabolic rate. Differential diagnoses can be established only after complete and diversified study of the case, interpreting subjective evidences in the light of objective facts.

The endocrine glands are among the important regulators of metabolism. It is not remarkable then that disturbance of two wholly unrelated foci of control may produce a common end result. The cheery optimism of the speculative endocrinologist who sees a definite endocrine element in some obscure condition because of a single symptom also associated with some classic endocrine syndrome, does not make for progress. That

*This statement does not imply a failure to recognize the vast amount of animal experimentation involving the suprarenal bodies. So much of this work, however, is inapplicable to human problems involving these glands that, in this restricted sense, the above statement is felt to be warranted.

many hypothyroid subjects exhibit obesity, does not connote a thyrogenic origin of all obesity. Due tribute must be paid to what may be euphemistically designated as a hearty appetite, to say nothing of the several pathological obesities in which the thyroid has no part. The promiscuous and injudicious use of thyroid extract to combat this conditions has, like King David, slain its tens of thousands. The presence or absence of thyroid enlargement is absolutely no criterion. Severely toxic and practically inert thyroids of normal size are observed daily, while the massive hyperplasias of the endemic goiter frequently are associated with a completely normal bodily function. The tale could be lengthened indefinitely, but enough has been said to indicate that the diagnosis of atypical, incipient, and obscure thyroid conditions requires a most careful and complete differential survey. The exclusion of non-endocrine disorders is no less important than the inclusion of an hormonic aberration, and should precede it.

As is patent from the character of the data, and as has already been stressed (2), the presentation, in collected form, of data inherently self-contradictory, offers difficulty. Averages can be employed only when the composing units have the same sense and differ only in magnitude. An average composed from a judicious selection of + and — observations, could only present a wholly misleading normality. On the other hand, case series must be of sufficient length to merge individual differences of extraneous origin and indicate the true trend of the observation. For purpose of clarity in presentation and waiving the nice points of an ever active controversy, in the following discussion we shall designate as "hyperfunctional" (+) all cases presenting a uniform picture of what is generally regarded as an over-activity. Conversely, "hypofunctional" (—) cases present the antitheses of the foregoing. The intermediate group, in which are merged individual symptoms portrayed by the two extreme conditions, we shall designate as "dysfunctional" (±). In this later group are to be found those cases in which an initial hyperactivity is undergoing a functional involution (transition states) with an unequal rate of recession of the several salient characteristic features. In taking this position, we hope to avoid argument that can only obscure the principal aim of the thesis. Incidentally, this attitude is a not uncommon one among the serious workers in this field.

OBSERVATIONS

Following a practice established in the earlier papers, first consideration will be given to the physical measurements of the several groups. The data are collected in Table I.

TABLE I

Physical Measurements

Observation	Unit	Gland Function —	Gland Function ±	Gland Function +	Grand Average
Number of Cases		**126**	**53**	**21**	**200**
Sex—Male	%	**29**	**17**	**33**	**27**
Female	%	**71**	**83**	**67**	**73**
Age—High	Years	74	66	70	
Low	Years	8	8	18	
Average	Years	**37**	**33**	**44**	**37**
Height—High	cm.	189.5	181	176	
Low	cm.	134	131.5	148.5	
Average	cm.	**164**	**159**	**165**	**163**
Sitting Height—High	cm.	97	93	93.5	
Low	cm.	71.5	73.5	80.5	
Average	cm.	**87**	**85**	87	86
Sitting Height Index		**0.530**	**0.535**	**0.527**	**0.531**
Chest—High	cm.	150	99	93.5	
Low	cm.	57	64.5	62.5	
Average	cm.	**83**	**77**	**78**	**81**
Weight—High	kgm.	156.6	100.0	73.8	
Low	kgm.	30.6	31.3	40.8	
Average	kgm.	**65.1**	**59.5**	**58.7**	**62.9**
Area—Average	sq.m.	**1.71**	**1.61**	**1.65**	**1.68**
Lung Volume—High	cc.	5380	3720	4600	
Low	cc.	1100	1350	820	
Average	cc.	**2840**	**2570**	**2310**	

The allocation of cases to the several groups offers a statistic that is potentially misleading. The cases here presented were seen in the course of a consulting diagnostic service. Hyperactivities of the gland are usually too well defined to require elaborate analysis for diagnosis. Our studies on this group lack certain of the tests comprehended in the usual case analysis, and for this reason have been omitted from the tables including them. The relative proportion of dys- and hypo-functional cases to each other is probably more representative.

The dominant incidence of thyroid disease in the female has been noted by many (4, 5), the Mayo Clinic reporting 85 per

cent females in nearly three thousand cases, while Sattler's compilation shows an equal (82 per cent) incidence. The same general trend is manifest in the hypo-functional group, though sex disparity is much less in the hypothyroidism of childhood. The age averages possibly show the tendency for the hypofunctional condition to occur earlier in life, but the lower average age of the dysfunctional group (containing many transition cases) is inharmonious. With thousands instead of hundreds of cases these discrepancies would probably disappear. The practical elimination of young cretins from this series certainly raises the average age of our hypofunctional group. This same factor undoubtedly operates in fixing certain of the other measurements, notably the standing height, at the relatively normal levels observed. In fact, our data are to be regarded as giving a picture of the incidence of thyroid disease in adult life when certain of the growth inhibitions are no longer operative. The weights here recorded, on an average, do not indicate the dominance of obesity usually associated with decreased function. The inclusion of a number of the thin amyxedemic thyroid failures—a syndrome identified by us and to be described later in this paper—unquestionably influences the average and renders it less representative of the classic type. The extremes observed for the several measurements are significant, and it is perhaps pertinent, in the light of the foregoing, to call attention to the fact that both the highest and lowest absolute values are found in the hypofunctional group. In some instances, relative exceed absolute values in significance, and in the next table are given the weight-chest-lung volume comparisons made under conditions outlined in the first paper.

Over one-third of our outspoken thyroid failures are underweight, although in deriving a net average for the group they are completely absorbed. These several net averages show a tendency from group to group, as do the relative percentages of the moieties of each above and below the predicted values. The chest measurements give no evidence of the characteristic distribution of weight, although, as has been shown earlier, the female chest-hip ratio exhibits significant differences.

The average thyroid subject shows a loss of lung volume from the predicted level which is truly significant. Bryson's (6) observation that chest expansion is limited, may bear upon

this finding. That it is not solely due to fatty infiltration, as claimed by Askanazy (7), is demonstrable by comparison with the obese of other than thyroid origin. The full magnitude of the deviation in many cases is somewhat obscured in our averages by the inclusion of a significant number of incipient cases. A marked loss (40 to 60 per cent) of predicted lung volume is a common finding in cases offering no other cause for the phenomenon than the thyroid disease.

TABLE II

"Vital Capacity"

Observation	Unit	Gland Function −	±	+	Grand Average
Weight—High	%	+247	+78	+27	
Low	%	−38	−29	−25	
+ Average	%	**+23**	**+19**	**+13**	
%	%	64	56	43	
— Average	%	**−14**	**−11**	**−14**	
%	%	36	44	57	
Net Average	%	**+10**	**+6**	**−3**	**+7**
Chest—High	%	+96	+26	+17	
Low	%	−21	−15	−23	
+ Average	%	**+12**	**+11**	**+7**	
%	%	64	47	62	
— Average	%	**−7**	**−6**	**−12**	
%	%	36	53	38	
Net Average	%	**+5**	**+2**	**±0**	**+4**
Lung Volume—High	%	+19	+25	+6	
Low	%	−70	−47	−75	
+ Average	%	**+6**	**+13**	**+6**	
%	%	11	8	5	
— Average	%	**−25**	**−25**	**−41**	
%	%	89	92	95	
Net Average	%	**−22**	**−22**	**−39**	**−24**

Such urine findings as may be offered in tabular form are grouped in Table III.

The urine volume has a somewhat downward tendency, and the total elimination in the hypofunctional group tends to be inadequate. Coupled with this is a high incidence of small amounts of albumin and, as will be seen later, a blood picture suggesting retention. To these general indices we have applied the term "pseudonephritis," as other signs of kidney impairment are wanting and both the blood and urine picture attain

to a continued normality under treatment. Falta (8) comments on the small volume and slight albuminuria, and ascribes them to nutritive disturbances of the kidneys. Another possible explanation might be a deposition of the mucin-like substances that have been identified in other parts of the body and in the kidney by Halliburton (9) and others. Broadly speaking, lowered elimination, slight albuminuria, and not infrequently the appearance of casts, is generally recognized as of relatively high incidence in the several forms of thyroid disease. Our own figures would seem to indicate a tendency toward their appearance with failing thyroid function.

TABLE III
Urine Measurements

Observation	Unit	Gland Function —	±	+	Grand Average
Volume—High	cc.	4350	3090	2060	
Low	cc.	340	360	470	
Average	cc.	**1090**	**1050**	**1090**	**1080**
Spec. Grav.—High		1.036	1.036	1.028	
Low		1.002	1.007	1.007	
Average		**1.019**	**1.021**	**1.019**	**1.020**
Albumin	%	**29**	**25**	**11**	**26**
Casts	%	**16**	**21**	**11**	**17**
Sugar	%	**7**	**17**	**16**	**11**
"Urobilinogen"*	%	**5**	**3**	**0**	**4**
Amylase Index—Av.		17	15	—	
Salol—Av.	min.	**103**	**70**	—	**91**
Urea Curve—Normal	%	67	70	—	**67**
Delayed	%	4	20	—	**8**
Progressive	%	4	0	—	**3**
Low	%	25	10	—	**22**
Phenol-Sulphone-Phthalein, 2 hour Elimination—Av.	%	**53**	**57**	**59**	

*Positive tests due to concomitant liver involvement. See text.

The question of glycosuria is a moot point and one that even today is far from a state of general agreement. As early as 1907 v. Noorden (10) commented on an occasional appearance of sugar in the urine of myxedemics—this, too, in a condition generally recognized as raising the sugar tolerance. Falta (8) cites a personal observation at some length of a myxedemic who showed slight alimentary glycosuria even after treatment had been suspended for two months. He infers simultaneous pancreatic involvement, also a possible complicity of the hypophysis, and offers this explanation to account for the same carbohydrate anomaly

as reported by several other observers. Blood sugar values are lacking. Several other explanations offer themselves as being, at least, equally plausible. First, if it be conceded that the thyroid exercises any control over carbohydrate metabolism—and this is scarcely a debatable point—it must be remembered that many cases are seen of patients in a transition state between an earlier hyper- and a final hypo-activity. As all of the functional disturbances characteristic of the first state do not recede with the same velocity, a picture inevitably results which lacks the definition of either of the initial or terminal phases and

TABLE III-a

		Basal Met.	Gal. Tol.	Blood	Remarks
No.	Sex	Dev.	Dev.	Sugar	
B-169	F	—20	±0	102	
234	M	—11	±0	92	Earlier thyrotoxicosis (Goiter).
267	F	—10	+25%	94	Earlier thyrotoxicosis (Goiter).
528	M	—29	±0	100	Psychosis (manic depressive).
559	F	—26	±0	83	Obesity.
S-531	F	—13	—	83	Pregnant. Had been under intermittent Thyroid medication for years.
640	F	—21	Incomplete Not < N	104	Otosclerosis.
685	F	—16	±0	133	Blood sugar level due to emotion. Patient nervously very unstable. which fact probably influenced the observed basal rate to some extent.
1013	F	—26	Incomplete Not < N	100	Sterile. Became pregnant after thyroid medication.

includes features of both. A full discussion of this question is shortly to appear elsewhere, and in the interest of brevity will here receive no further mention. A second possibility in Falta's case, as well as others simulating it, lies in his report of an earlier jaundice. Scattered through the literature are occasional references to liver disorders complicating thyroid disease. We shall discuss such a group in a subsequent portion of this paper. It is well known that certain types of liver involvement lower the sugar tolerance to a very appreciable degree. Frankly, in Falta's case the liver would have to be excluded before credence could be given to the complicity of a multiglandular concert.

In the present instance, because of the diversity of opinion on this point, a further analysis of the anomalous cases may be permitted. This can be confined to the pure hypofunctional group, as the anomaly really exists only with its composing members. The significant facts can be offered most compactly in tabular form.

Of the nine cases presenting, three subjects, namely, B-234, B-267, and S-531, can at once be eliminated as the first two have histories of earlier hyper-activity, and the third is pregnant. The first two are included in the hypofunctional group as the glycosuria represents the only departure exhibited, and the residual picture was clear-cut thyroid failure. The other six cases all show normal blood sugar levels and a galactose tolerance that in no case is below normal. True, the metabolism of galactose varies in some measure from that of glucose, and the urine sugar is presumably the latter. In any case, there is nothing here to support either a pancreatic or hypophyseal complication. In all of the "B" cases the liver is ruled out by other observations, and in the "S" cases, by the implication of the normal sugar tolerance. As before stated, this question will be discussed elsewhere under more elastic space conditions.

TABLE IV

Nitrogen Partition

Observation		Unit	Gland Function —	±	+	Grand Average
Total Nitrogen	Av.	gms.	8.32	8.59	8.79	8.44
Urea Nitrogen	Av.	%	78.6	80.5	78.0	79.1
Uric Acid Nitrogen	Av.	%	2.6	2.1	2.2	2.4
Ammonia Nitrogen	Av.	%	4.0	3.8	3.9	3.9
Creatinin Nitrogen	Av.	%	4.3	4.4	3.6	4.3
Residual Nitrogen	Av.	%	10.5	9.2	12.3	10.3
%=or < 9%		%	64	54	67	61

"Urobilinogen," the probably non-specific response to the paradimethylamino benzaldehyde reagent of Ehrlich (11) was demonstrated only in cases exhibiting a concomitant liver disturbance. This will be discussed later. The urea curves synchronize well with the earlier evidences of loss of renal integrity which, however, the phthalein test fails to support. That this latter test is subject to many sources of error is recognized. Further, in the lowered permeability in many of these cases

there is not the loss of renal function that certain of the tests would imply. The delayed elimination of salol falls in this category rather than in that of a lowered gastric motility.

A complementary observation of urine composition comes in the determination of the formula of nitrogen distribution.

The average nitrogen elimination is low, both in comparison with other endocrine and with non-endocrine disorders. As these data represent typical 24-hour collections on the patient's usual diet, and not nitrogen metabolism experiments, they cannot be equated directly with the careful studies of Janney and Isaacson (12). They would certainly seem to confirm the latter's contention in regard to the rate of protein destruction in thyroid disease. If relative weights are considered, these data offer no support of Forschbach's (13) contention that the creatinin elimination is decreased in hyper-active states. The accuracy of this has previously been denied by others.

The relation of the other measured quantities accords well with accepted normal standards. Only the residual portion departs from convention, and that registers a level definitely superior to the established norm. Moreover, this increase is shown by three-fifths of the entire group of cases. That it is not due solely to the presence of creatin, as noted by McCrudden (14) and others, has been observed by one of us (15). Rather, there exists nitrogenous material of unknown composition which is demonstrable not only in the endocrinopathies, but in other pathologic conditions as well. Of the entire group of endocrine disorders, the thyroid shows the generally highest level of this quantity, both in average amount and frequency of incidence of fractions exceeding the conventional normal. It constitutes an important datum in the general compilation of facts leading to diagnosis.

Earlier in the paper we have spoken of the pseudonephritis frequently observed in cases of thyroid failure. The urine findings have already been discussed; the blood chemistry next claims attention.

Inspection of the average values given above would not seem to confirm the statement that the blood gives evidence of retention. Two points, however, must be borne in mind. First, the level of protein metabolism in these cases is low as gauged by the total nitrogen of the urine. In the light of careful metabolism

studies, among others of Boothby and Sandiford (16), and Janney and Isaacson (12), this would seem to be due to diminished intake and absorption rather than to any characteristic change in the catabolic phase. It is demonstrable that low protein metabolism lowers levels of blood nitrogen, just as high utilization determines increase. The blood picture, however, varies

TABLE V

Blood Chemistry (and Serology)

Observation	Unit	Gland Function —	±	+	Grand Average
Non Protein Nitrogen	Av. mgm.	31	33	29	31
% > 35 mgm.	%	28	30	6	25
Urea Nitrogen	Av. mgm.	16	15	15	16
% > 17 mgm.	%	23	18	20	22
Uric Acid	Av. mgm.	3.6	3.4	3.6	3.5
Net[1] % = or > 4 mgm.	%	20	14	22	19
Creatinin	Av. mgm.	1.4	1.5	1.5	1.4
Residual Nitrogon	Av. mgm.	13.2	16.3	12.2	15.3
Sugar	Av. mgm.	96	102	97	97
% > 120 mgm.	%	1	6	5	3
% < 80 mgm.	%	6	0	11	5
+Wassermann	%	0	0	5	0.5
+Kahn (presumptive)	number	0	0	0	
+Spinal Fluid	number	1[2]	0	0	1
+Schwartz-McNeil	number	0	0	0	

[1] All demonstrated cases of nephritis and gout have been deleted.
[2] Non-luetic.

within much narrower limits than may be conditioned by the protein exchange.* Second, individual cases showing relatively high values lose their identity when merged by averaging with a number of observations which do not exhibit the condition. The significance of relative values should be stressed. A non-protein nitrogen of 35 mgm., absolutely normal by accepted convention, is relatively high for an individual excreting less than 6 grams of nitrogen in twenty-four hours. Further, one-fourth of the cases of this series showed values for non-protein nitrogen in excess of 35 mgm., paralleled by an almost equal incidence of urea nitrogen values in excess of the conventional norm. Fifty cases showed uric acid equal to or above 4 mgm., but of these, eighteen gave other evidences of true nephritis and are deleted in the tabular presentation. The contention, then, has a measure

*One of us (Rowe and Walker, unpublished data,) has produced changes of blood nitrogen of the order of 15-20 per cent in normal subjects by adding from 100 to 200 per cent of additional protein to a maintenance ration.

of reason when due allowance is made for the limitation of this form of presentation.

A point of interest, for which we can offer no explanation at present, is the somewhat low value of the residual nitrogen in the terminal groups. The somewhat high value of the dysfunctional cases brings the total average to a normal value.* Of the several blood constituents, the sugar is the only one which has received any extended record in the literature.

This is presumably due to the influence of the thyroid on carbohydrate metabolism and the general use of the sugar curve method to determine tolerance. Sharp differences of opinion as to the fasting level of blood sugar and the complication introduced by comparison of fasting levels with those resulting from sugar alimentation, has stimulated study, albeit, in some instances, of a somewhat uncritical character. Without detailed analysis of the somewhat diffuse literature, it may be said that a careful survey would seem to indicate no hyperglycaemic effect of thyrotoxicosis in man, and, equally, a slight hypoglycaemic tendency in thyroid failure. The figures given above show that the averages of all three groups conform straitly to the conventional normal. This is even more strikingly illustrated by a selection of extreme cases drawn from the above group and collected in Table V-a.

TABLE V-a

Blood Sugar Levels

Observation			Hypo-function —	Hyper-function +
Number of Cases			24	7
Basal Metabolism Deviation—	High	%	—30	+87
	Low	%	—50	+44
	Average	%	—36	+65
Blood Sugar (fasting)—	High	mgm.	115	108
	Low	mgm.	71	78
	Average	mgm.	91	92
Number below 80 mgm.			5	1

Inspection of the figures given above fails to demonstrate any specific thyroid influence on blood sugar levels. True, these selected averages are lower than those of the entire groups, but

*Calculation of a large number of analyses of normal bloods would fix 15 mgm. as a fair average with a ± variation of perhaps 2 mgm. On this basis all of the values fall within the normal range.

it must be remembered that these cases represent the maximum of nutritional disturbance and hence a lower nutritional level. Not impossibly, a failure to take due cognizance of the importance of the level of nutrition prior to a sugar test is responsible for some of the conflicting data elsewhere reported. Faulty technique is another definite factor. The cases here recorded were, in the main, on a liberal, standardized diet for a period of at least four days before the blood sugar levels were determined. Further, only morning fasting bloods were taken, the foodless interval approximating fifteen hours.

Reverting to Table V, it will be noted that one of the hyperthyroid subjects gave a positive Wassermann reaction. The case was one of well-marked, typical exophthalmic goiter, with all of the classic signs. The luetic element here is concomitant only as affecting the general picture. In a second patient, the positive spinal fluid gave a gold curve of the meningeal type. No luetic element could be demonstrated or elicited.

In contradition to the blood chemistry, numerous observations exist on the influence of thyroid disease on the blood morphology. The earlier reports tend to stress an anaemia in Graves' disease, leucopenia and an increase in the lymphocytes and monocytes at the expense of the neutrophilic elements. Likewise, descriptions of the myxedemic picture reiterated the anaemia, leucopenia and lymphocytosis. Later observers have failed to confirm these findings in their entirety, and in several points there still exists a marked difference of opinion. In the first instance, Plummer (17) in a long series has failed to confirm the monocyte increase and the leucopenia. There is a slight anaemia, tendential rather than established, and a moderate relative leucocytosis. Our own data are assembled in Table VI.

In all of the groups the values for haemoglobin and erythrocytes are normal, although tending downward. Lymphocytosis is found throughout, although the distribution is opposite to that observed by Falta, who found it more pronounced in the hyper-active cases (8).

Likewise, the eosinophilia recorded by him is not manifest, nor do the monocytes exceed the limits of normality. While it is generally recognized that the blood picture does not correlate with the severity of the condition, an analysis of the same group

of extreme cases, collected in Table V-a, may not be devoid of interest.

These values equate well with those of the preceding Table (VI), although slight differences are apprehensible. The anaemic

TABLE VI
Blood Morphology

Observation		Unit	Gland Function —	±	+	Grand Average
Haemoglobin	Av.	%	87	87	88	87
Erythrocytes	Av.	10^6	4.84	4.87	4.94	4.87
Color Index			0.90	0.89	0.89	0.90
Leucocytes	Av.	10^3	7.5	8.2	7.2	7.7
P. M. N. Neutrophiles	Av.	%	56	57	60	57
%=or > 75%		%	2	12	5	
Lymphocytes	Av.	%	38	35	33	37
%=or > 33%		%	66	54	43	60
Eosinophiles	Av.	%	2	2	2	2
Net %=or > 3%[1]		%	19	27	11	20
Monocytes	Av.	%	4	6	5	4

[1] Cases in which a non-endocrine cause of eosinophilia was demonstrated have been deleted.

tendency is slightly more marked, the leucocytes are slightly lower, and the monocytes and lyphocytes higher in the hyperactive group. Barring the monocytes, our figures agree well with those of Plummer, which carry conviction, as they are based upon nearly one hundred times as many cases. With the hypoactive cases, the leucocyte value is even more normal, the lymphocytes go to a slightly higher level, the monocytes remain unchanged. A slight increase in eosinophiles brings this point

TABLE VI-a

		Hypofunction	Hyperfunction
Haemoglobin	%	87	84
Erythrocytes	10^6	4.71	4.59
Leucocytes	10^3	8.0	6.7
Neutrophiles	%	52	55
Lymphocytes	%	41	37
Eosinophiles	%	3	1
Monocytes	%	4	7

more nearly in accord with Falta's observations, but falls far short of the really significant magnitudes recorded by him.

Seemingly, the lymphocytosis is the only point of real departure from the generally accepted normal adult picture, and

this is found in practically all of the endocrine states and in not a few non-endocrine disorders. The magnitude of the relative increase is somewhat greater in thyroid than in the other named conditions.

The respiratory metabolism and its usual expression in the basal metabolic rate, constitutes a chapter of the greatest importance in the diagnosis of thyroid malfunctions. Taken as a sole criterion, usually it is wholly inadequate to establish a diagnosis; considered as one observation in a group, it probably has more individual significance than any other single test, with the possible exception of the sugar tolerance. And this statement presupposes a careful and complete clinical analysis of the case as intrinsic in any diagnostic procedure.

From the initial observations of Magnus Levy (18) that thyroid disorders were associated with marked changes in the oxygen consumption, an extensive literature has come into being. In the interest of brevity, no attempt will be made to review the earlier work; the discussion will be confined to our own observations, since they constitute a part of the general diagnostic scheme. The data are found in Table VII.

Following the convention earlier defined, we find the uncomplicated hypoactive states showing an oxygen consumption rate equal or inferior to 10 per cent below the predicted value. Similarly, the established hyperfunctional cases range from +19 to +87 per cent. The points of emphasis lie in the direction of the change, and more importantly in the amount. While other disorders may condition significant changes, but few approach in magnitude those of thyroid origin. And with these—diabetes with great emaciation and Addison's disease on the one hand, and the leukaemias and high fever on the other—a few relatively simple additional observations will permit of a ready differentiation. As has been discussed elsewhere (2) of the endocrine concert, only the adrenal approaches the level of myxedema in its failure, and even here it falls appreciably short of the low levels which severe thyroid inactivity can engender. While the lowest level recorded in this series is —50 per cent, we have recorded cases falling nearly 10 per cent lower. A few similar observations have been recorded by others.

The blood pressure values show a definite gradation in the sense of the basal rate. The picture in the hypothyroid group

is complicated by the fact that in the later stages arteriosclerosis tends to raise blood pressure from the initial low to a final hypertensive level. In any average such as the present, which includes all chronological phases, a few arteriosclerotics will raise the average appreciably. This is well illustrated in the sequence of the percentages of low values for the systolic pressure. As is to be expected, the diastolic readings are less influenced. The

TABLE VII

Respiratory Metabolism

Observation	Unit	Gland Function —	±	+	Grand Average
Basal Metabolism Deviation High	%	—10	+18	+87	
Low	%	—50	—31	+19	
+ Average	%	—	+11	+42	
%	%	0	19	100	
— Average	%	—24	—14	—	
%	%	100	81	0	
Net Average	%	—24	— 9	+42	
% > +10 %	%	0	6	100	
% between +10% & —9%	%	0	39	0	
% = or < —10 %	%	100	55	0	
Blood Pressure:					
Systolic Av.	mm.	114	120	138	
% < 110 mm.	%	54	32	10	
Diastolic Av.	mm.	71	74	70	
% < 65 mm.	%	33	26	50	
Pulse Rate: Av.	Per min.	66	79	101	
% = or < 80 per min.	%	8	45	81	
% = or > 70 per min.	%	70	21	0	
Respiration Rate: Av.	Per min.	15	16	18	
% = or < 10 per min.	%	9	4	10	
Temperature: Av.	Deg. F.	97.7	98.2	98.2	98.0
Alveolar CO_2: Av.	mm.	39	38	37	38
% > 35 mm.	%	78	65	67	74
% = or < 30 mm.	%	5	8	14	7

pulse rate sequence is also striking and of the order to be expected. Very slow heart rates are usually associated with established failures, although with mounting blood pressure there is a tendency for the pulse to augment. These trends do not synchronize, however, and constitute one of the several elements leading to the contradictory picture of the transition state. The rapid breathing, frequently concomitant with the tachycardia of Graves' disease, finds tendential expression in the values given above. Likewise, the hypothermia of the established failure is

indicated. It must always be borne in mind, as earlier noted, that in any compilation such as the present, the extreme findings of the terminal state are minimized materially by the inclusion of the incipient and developing cases. Trends, therefore, take on an added significance.

The prevailing tendency of the alveolar CO_2 tensions is toward the normal. The sub-normal tensions observed are possibly influenced by the measure of the patient's co-operation,* and in the over-active cases rapid breathing may condition some CO_2 deficit. The Fredericia method was used throughout, earlier

TABLE VIII

Galactose Tolerance

Observation	Unit	Gland Function —	Gland Function ±	Average
Male				
Dose: High	Gms.	40	30	
Low	Gms.	30	20	
% above normal	%	13	0	
Average deviation of dose	%	+33	—	+33
% equal normal	%	87	33	
% below normal	%	0	67	
Average deviation of dose	%	—	—33	—33
Female				
Dose: High	Gms.	60	40	
Low	Gms.	40	20	
% above normal	%	33	0	
Average deviation of dose	%	+31	—	+31
% equal normal	%	67	63	
% below normal	%	0	37	
Average deviation of dose	%	—	—29	—29
Summary				
% above normal	%	25	0	18
% equal normal	%	75	56	69
% below normal	%	0	44	13
Average + Deviation (1)	%	+32	—	
Average — Deviation (1)	%	—	—31	

(1) Not weighted for relative number of cases.

study (19) having demonstrated its relative dependability. Failure to expel the air thoroughly will give a sample diluted by the tidal phase.

The last laboratory observation to be considered, the sugar tolerance, equates with the basal rate in diagnostic importance—and is equally unfitted to be a sole and final arbiter.

For reasons which have already been discussed, galactose was selected as the vehicle for the tolerance test. That it un-

*In a few cases it was possible to demonstrate this element.

doubtedly has a different metabolic cycle from glucose may be freely admitted. The chief aim was, however, to devise a sugar tolerance test which should be simple, easily applied, and, most importantly, clear cut in its indications. That galactose complies with these criteria has been amply demonstrated, while the intrinsic differential sex influence is an added advantage of great value. The majority of observations of sugar tolerance are based on glucose studies, and the greater part of these on the blood sugar curve method. As one of us (20) has shown, the so-called diagnostic curves of hyper- and hypo-thyroidism are readily reproducible in a group of established thyroid failures, or equally with normal subjects, by the use of dosages above or below the utilization capacity of the given individual. For example, Olmstead and Gay's (21) two differential curves were reproduced by us in a single group of myxedemics by the use of sub- and supertolerance doses. The shape of the blood sugar curve is determined by the relation of the dose given to the individual tolerance, and at the best is but qualitative in its indications. The lack of dependence of the reaction to the test meal upon body weight has been stressed. For example, if the Janney and Isaacson technique (22) were followed in case of myxedemics whom we have studied and who were identical in all respects except body weight, one would have received 84, the other 218 grams of glucose. As it was, one responded to 40, the other to 50 grams of galactose. The curves elicited by test meals based on weight could not fail to be misleading in any quantitative sense.

The inclusion of quantities of other foods and of the juice of grapes or the citrus fruits is so patently undesirable as to require no discussion.

Review of the literature shows a variety of contradictions, but in the main it may be said that in existing hyperthyroidism the sugar tolerance is diminished, while the reverse obtains with the opposite terminal condition. Definite quantitative expression is usually lacking. Hirschl's (23) report of the failure of 500 grams of glucose to excite glycosuria in a group of myxedemics, equates with some of Miura's (24) observations. The interest here is in the physiological phenomenon of the retention of these massive doses rather than in a quantitative significance of the test.

Of tests with galactose, but few are recorded. Bauer (25), using 40 grams and requiring for his standard an elimination in excess of 3 grams, found two positive in nine cases of hyperthyroidism. Wagner (26), with the same dosage but positive response indicated by one gram, reported thirteen out of fourteen as positive. Strauss (27), with 30 grams, and Hirose (28), with 25, both using a qualitative urine test as the criterion of response, found, respectively, three in four and nine in nine to be positive in thyrotoxicosis. Neubauer (29) tested a group of cases after thyroidectomy, using 40 grams and an elimination greater than 0.9 grams as the criterion. Thirty-eight out of forty-five were positive, and only two failed to show some sugar.

Our own findings agree in sense with the foregoing, but differ widely in the quantitative expression. For reasons given in the table, no established cases of hyperthyroidism appear. A few isolated records, made in connection with other studies, would seem to indicate that the established hyperthyroid case exhibits either a normal or slightly depressed tolerance for galactose, of the same order of magnitude as observed in the dysfunctional group. This statement is tentative and is open to revision should an extended series of observations indicate necessity. Present information warrants the conclusion given above. Perhaps the most striking feature of the results is the dominantly large percentage showing a normal tolerance. Further, where deviation does occur, it is of a very moderate order in the uncomplicated cases. A few of our observations have been omitted from the general tabulation, as their inclusion could only serve to mask the general trend, and in each instance the anomaly was directly traceable to a non-endocrine cause influencing carbohydrate metabolism. The cases severally were those of one male giving positive response with 20 grams (a —33 per cent of deviation), and four women averaging a deviation of —68 per cent. They were all demonstrated thyroid failures and all equally had a demonstrated liver disorder to which the lowered tolerance was directly referable. In this connection it may not be inapposite to recall the fact that the first use of galactose for function testing was by Bauer (30) in 1906, and was offered as a means of evaluating liver involvement.

To summarize then, the status of galactose tolerance in thyroid disorders: Over two-thirds of the subjects show a normal

tolerance. When extraneous effects influencing tolerance can be excluded, the dose producing melituria, if altered, moves in opposite direction to the basal rate change and is always of moderate amount. These results agree qualitatively with other observations, but differ materially in the quantitative expression. The differential significance of this fact is patent.

There is yet another point in connection with the carbohydrate metabolism that may well be touched upon at this time. Earlier in the text, note was made of the occasional appearance of glycosuria in patients with demonstrated thyroid failure, seemingly uncomplicated by other factors which might influence the sugar assimilation limit. From the foregoing discussion, it is evident that the thyroid influence on carbohydrate metabolism in general is definite, but of a lesser order of magnitude than that of the pancreas, the pituitary or the adrenal. In a few cases, however, of unmistakable exophthalmic goiter, we have observed a profound influence on the assimilation limit usually associated with relatively small changes in the respiratory metabolism. The protocol of a typical case will be given and discussed in a subsequent portion of this paper. A possible explanation of the apparent anomaly could lie in the existence of a second thyroid hormone exercising an influence on sugar metabolism as does thyroxin, or its analogue, on the consumption of oxygen. This suggestion is offered tentatively; it will be discussed later in the paper.

PART II. CLINICAL SECTION

INTRODUCTION

The clinical section of this paper is based upon the analysis of a series of 100 consecutive cases which comprise part of the larger series reported in the previous section. The reasons for selecting the smaller group for clinical analysis are: First, that all the patients in it have been under the personal observation of one of us for sufficient time to demonstrate the effect of treatment, confirming the diagnosis; and, second, that the series can be fairly compared with an equal number of cases of pituitary failure already reported. All the cases reported here repre-

sent thyroid failure, as demonstrated by the laboratory findings and response to treatment. Cases of hyperthyroidism and dysthyroidism have been excluded for the sake of clearness and brevity.

SOCIAL AND FAMILY HISTORY

Social History: The social history of these patients does not yield any new information of value in regard to thyroid failure. It is nearly impossible to make a fair and accurate division as regards nationality, since the mixture of races is so complete. Also, because of the mobility of population, it is impossible to separate patients into significant groups as regards geographical factors, since many individuals have lived in, and outside of, goiter belts for varying periods of their lives. In individual cases, the patient's birthplace and residence may be relevant, but in a large series such factors are not significant. Of this series, 97 per cent gave their nativity as "American." In the majority of these the names were Anglo-Saxon, with a definite minority suggesting Irish or Jewish parentage.

Sex: Division as regards sex shows that slightly over one-fourth of our patients are males (see Table I). This agrees with Biedl's (31) figures, but is rather higher than those of Dock (31). All are agreed, however, that hypothyroidism occurs more frequently in women than in men, but that the condition is not extremely rare in the latter. There is no satisfactory explanation of the fact that the female is three or four times more liable to disturbances of thyroid function than the male. It seems possible, however, that this preponderance is due to the alterations in metabolism incident to pregnancy. The female thyroid possesses a potential variation of function not demanded of the male, and this potential variation may cause the lack of stability which seems to distinguish the female from the male gland.

Age: Our figures as to age distribution differ slightly from those by Boothby (31) at the Mayo Clinic. Of his 89 cases, 73, or 82 per cent, were between thirty and sixty years of age, while in our 100 cases, only 52 per cent were between those ages, and 41 per cent were less than thirty years old. Possibly the difference may be due to the fact that Boothby's patients were "myxe-

demics," which signifies the presence of myxedematous accumulations as one basis for the diagnosis, while our series includes all patients with hypothyroidism, as demonstrated by our examination and treatment, regardless of the presence or absence

TABLE IX

AGE INCIDENCE

1-10 years	2%
11-20 years	19%
21-30 years	20%
31-40 years	17%
41-50 years	17%
51-60 years	18%
61-70 years	4%
71-80 years	3%

of myxedema. It may perhaps make for clearness if we state at once that in our opinion myxedema is not a sine qua non of thyroid failure, and that its presence in any patient depends, not so much upon the degree of thyroid depression, as upon coexisting circulatory and renal arteriosclerosis. Naturally, the symptom, if such be its origin, would be much more common in middle and later life than in youth, and the difference between Boothby's figures and ours becomes, on this basis, quite logical.

TABLE X

FAMILY AND SOCIAL HISTORY

Family Record	
Abnormal weight	8%
Abnormal height	6%
Diabetes	7%
Goiter (unclassified)	11%
Thyroid failure	16%
Acromegaly	0%

Inheritance: In nearly half of our patients there was a history suggesting endocrine disease in the family. In 27 per cent there was definite proof of thyroid disturbance, as shown by goitre or proven thyroid failure, and in 7 per cent there was a

reliable history of diabetes mellitus. In some instances the family tendency was particularly striking. We have records of one family in which both father and son have undoubted hypothyroidism; in each of two other families both children are similarly affected, and in one family, consisting of father and three children (see later), all have been proven in our clinic to have thyroid failure, with basal metabolic rates ranging from —23 to —33 per cent. There can be no doubt that as Lisser (31) says, "Families may and do transmit a predisposition to disturbance of the endocrine system, just as some families exhibit a tendency to cardiovascular disease."

Marital States: Forty-three per cent of our patients were single, 57 per cent were married. The fraction of unmarried patients may possibly have the same significance that Davidoff (32) ascribes to analagous figures in his series of acromegalics, but it seems more probable that our rather high percentage of single patients is due to the effect of thyroid failure on the patient's personality, a point which will be discussed more fully later in this paper. The high incidence of sterility (22, or 39 per cent of the married group) will also be discussed under the symptoms of hypothyroidism.

TABLE XI

PAST HISTORY

Development	
A. Physical, normal	86%
Physical, abnormal	14%
Physical, delayed	9%
Physical, accelerated	5%
B. Mental, normal	94%
Mental, abnormal (delayed)	6%*
C. Sexual,†, normal	45%
Sexual, delayed	37%
Sexual, early	7%
Sexual, not stated	11%

*Four of the six showed coincident physical retardation.
†Females only. (See text.)

Physical Development: Only 14 per cent of our patients gave a history of disturbed physical development. This means that in only 14 per cent was the thyroid failure operative during

the period of growth. In our experience it is only in the cretins, in whom the lack of thyroid secretion probably exists from birth, that any marked influence of the thyroid upon development is demonstrable. This is in marked contrast to disturbances of pituitary activity, which affect growth as a rule, rather than as an exception.

Mental Development: Here again our figures for delayed mental development are certainly less than the truth, but they are significant as indicating that both mental and physical development are delayed or impaired if thyroid activity be depressed, whereas pituitary hypofunction, which also gives rise to delayed growth, has a much less marked effect upon mental development. The practical elimination of cretins from our series adds weight to this statement.

Sexual Development: Onset of Puberty. Exact figures for this event can be obtained only from female patients, there being no definite occurrence to mark puberty in a boy as does the appearance of the catamenia in girls. Our figures, therefore, represent only the females in our series. It is courting criticism to attempt to set arbitrary age standards for the normal appearance of menstruation, but for the sake of definite criteria, we have chosen 12 years as the early limit and the fourteenth birthday as the late limit for normal appearance of catamenia. On this basis less than half our female patients certainly began to menstruate during the normal period, and of those whose menarche was abnormal, delay was six times more frequent than precocity. Here again the depressing effect of thyroid hypofunction on development is more clearly apparent, and it is likewise demonstrated that delayed puberty demands careful investigation of the patient's endocrine system (particularly the thyroid and pituitary), if no organic disease can be demonstrated to explain the condition. That thyroid extract will correct the delayed sexual development due to hypothyroidism was beautifully demonstrated by one patient in our clinic. Born a cretin, her condition was early recognized and efficiently treated by Dr. J. J. Thomas of Boston. She came under our observation when she entered the obstetrical ward to be confined, and her past history disclosed the hypothyroid condition. Her menarche was only slightly delayed, her catamenia had been normal, and pre-

sumably she had escaped sterility by the early recognition of her condition and its efficient treatment. If medication is to be effective, it must be instituted during the growth period. It will not suffice to "wait and see" till the patient has passed twenty and then begin thyroid medication. The opportunity has then passed for normal development of the sex organs, and the result of such tardy treatment is almost certainly failure.

TABLE XII

PREVIOUS ILLNESSES

Mumps	47%
Tonsillitis	40%
Measles	23%
Scarlet Fever	23%
Pneumonia	15%
Diphtheria	12%
Typhoid Fever	8%
Emotional Strain	6%
Rheumatic Fever	3%
Trauma	2%
Tuberculosis	0%

PREVIOUS OPERATIONS

Tonsillectomy	40%
Appendectomy	5%
Cholecystectomy	1%
Hysterectomy	1%
Thyroidectomy*	1%

*There are a number of cases of hypothyroidism of surgical origin in the larger series.

Previous Illnesses: It was possible to demonstrate a definite connection between previous infections and thyroid failure in only scattered instances, and it is our belief that the acute infections are not generally patent factors in the production of hypothyroidism. The incidence of definite and severe chronic tonsillar infection in these patients is, however, prominent enough to suggest that it may be an important etiological factor. Forty per cent of our patients had had repeated severe sore throats and 32 per cent had had tonsillectomy. These figures are higher than those for measles, and nearly as high as those for mumps—both extremely common infections. The further fact that physical examination showed that in 32 per cent of our series the tonsils had been removed and that in an additional 24 per cent

they were definitely infected is significant of a not improbable connection between chronic tonsillar infection and depression of thyroid function. It has also been our experience that the removal of infected tonsils is a necessary preliminary step in the successful treatment of hypothyroidism. In several instances no benefit was obtained from thyroid extract pushed to the point of mild toxic symptoms before tonsillectomy, while the removal of the focal infection was followed by rapid response to a smaller dosage. It is no longer debatable that focal infection has a profound depressant effect upon bodily nutrition and function. How it produces this effect has never been determined, but it seems possible that it may be through the endocrine system and, more particularly, through a direct depression of thyroid or pituitary function.

TABLE XIII

DURATION OF ILLNESS

Less than 6 months	4%
Between 6 and 12 months	5%
Between 1 and 2 years	20%
Between 2 and 3 years	11%
Between 3 and 4 years	12%
Between 4 and 5 years	6%
Between 5 and 10 years	11%
Between 10 and 15 years	11%
Between 15 and 20 years	3%
More than 20 years	7%
"Always"	10%

Duration of Illness: The striking feature in the table showing the duration of thyroid failure in our series of patients is the long existence of the condition before it was recognized, a feature commented on by Blumer, Janney and others. To a certain extent the failure to make the diagnosis depends upon the insidious onset of the disease, and the lack of definite physical signs to account for the symptoms. In our opinion there is, however, a still stronger reason for the failure of physicians to recognize hypothyroidism. This lies in the general impression, derived from the name applied by Ord to the condition described by Gull, that there can be no really significant depression of thyroid function without the presence of demonstrable myxe-

TABLE XIV

PRESENT ILLNESS

Patient reported as a

Symptom:

	Chief Complaint	Definite Symptom
Menstrual disturbance	5%	54%
Exhaustion	59%	80%
Depression	3%	29%
Irritability	...	30%
Instability	5%	5%
Underweight	2%	32%*
Overweight	8%	21%*
Goiter	7%	14%
Deafness	5%	15%
Vertigo	4%	36%
Headache	8%	46%
Failing vision	1%	10%
Paræsthesias	4%	24%†
Insomnia	1%	16%
Appetite±	...	53%
Indigestion	3%	25%
Vomiting	1%	22%
Constipation	3	52%
Sterility	2%	39%‡
Impotence	7%	11%§
Menstrual disturbance	5%	54%
Diminished libido	3%	33%
Dyspnoæ	1%	28%
Palpitation	...	22%
Loss of hair	2%	30%

ADDITIONAL

Skin eruptions	12%
Diminished perspiration	40%
Hypothermia	41%
Marked change in weight	61%
Personality changes	63%
Loss of memory	7%
Urinary symptoms	14%

*Observed by measurement.
†Five cases severe.
‡Of 61 married.
§Males = 27.

dema. Therefore the possible existence of hypothyroidism never occurs to the average physician when myxedema is not demonstrable. In a previous paper (33) one of us has called attention to the fact that in a series of forty cases there was no significant difference in basal rate between those cases that showed myxedema and those that did not. The difference between the two groups lay in the ages and in the presence or absence of arteriosclerosis as determined by physical examinations, blood pressure determinations, renal function tests, and urinalysis. It was pointed out that arteriosclerosis was practically the rule in patients with myxedema, and was very rare in those who did not exhibit this condition. Our present series confirms the earlier findings and gives added support to the thesis that while there is no myxedema without marked hypothyroidism, there may be marked thyroid incompetence without myxedema, just as there may be marked renal incompetence without edema. If this be the case, it would be well to drop the use of the term myxedema as synonymous with hypothyroidism, since it seems to inhibit the early diagnosis of that condition.

Presenting Symptom: Reference to the chart brings out the fact that while the chief complaints of patients with hypothyroidism are many and varied, the outstanding symptom is general subefficient bodily performance, termed variously "exhaustion," "lack of endurance," "chronic fatigue," or "weakness." This symptom is, of course, the expression of the depressed metabolic activity incident to thyroid hypofunction, and is not due to organic change demonstrable by physical examination. Superimposed upon this expression of abnormal metabolism are a varied assortment of special complaints, indicating the effect of depressed thyroid activity upon practically all the various "systems" that compose the body. Prominent among them stands the nervous system, and because of the prominence of symptoms referable to it, many patients with hypothyroidism have had to carry for years the added handicap of a diagnosis of neurasthenia. It is true that neurasthenia, in its literal meaning is present, but before the term is applied to a patient in its medical sense, hypothyroidism as a possible basis for or aggravating factor of the neurasthenia, must be carefully considered. The tests which prove its presence or absence are so simple that

there is no justification for not applying them. The difficulty in the diagnosis of hypothyroidism lies not in the lack of a certain method of establishing it, but in the failure of the physician to consider it as a possibility in any given instance.

Whenever a patient complains of chronic fatigue or weakness, plus one or more of the symptoms enumerated in Table XIV, and physical examination fails to disclose organic disorder sufficient to explain the symptoms, that patient deserves such tests as are necessary to establish the presence or absence of thyroid or other endocrine hypofunction.

To do this, one measurement of the basal metabolic rate is not enough. There are other conditions that will depress basal metabolism, and these must often be eliminated by a combination of tests sufficient to embrace all the possibilities. As a rule, however, the symptoms enumerated, the absence of organic involvment, the presence of bradycardia, hypotension, hypothermia, changes in personality, malnutrition and abnormal weight, and the demonstration of a basal metabolic rate, properly determined, of —20 per cent or more, with an approximately normal sugar tolerance, is sufficient to establish the diagnosis and eliminate so-called neurasthenia.

Weight: This feature has already been thoroughly analyzed and deserves mention here only to emphasize the fact that underweight does not argue against hypothyroidism.

Loss of Energy: While this symptom was the chief complaint of only 59 per cent of our series of patients, it occupied a prominent place in the histories of eight out of every ten. It was variously described, but could always be translated into an expression of the inability of the patient to live a normal existence because of lack of energy to meet normal demands. This realization of subefficiency often results in the development of an "inferiority complex" and depression or hostility toward the world in general.

Psychoses: Definite psychosis was present in four of our patients, and in all was of the manic depressive type, the depressed phase being much the more prominent and of longer duration. Two of the four had attempted suicide; the other two had seriously contemplated it. All of them complained bitterly of their inefficiency and their inability to enjoy life. Two of the four have responded satisfactorily to thyroid medication, one

is improved but still has periods of marked depression, while the fourth is incooperative as to treatment and remains depressed. The so-called "neurasthenic" symptoms of hypothyroidism respond as a rule in a most dramatic manner to adequate treatment. Within a few weeks after the metabolism has been normalized by thyroid extract the depression and incooperative attitude disappear, and the patient's entire personality undergoes a marked change for the better.

Nervous System: Beside the psychiatric manifestations, symptoms suggesting organic disease of the central nervous system were numerous and prominent in our series of patients. Frequent headaches, often severe enough to be incapacitating, occurred in 46 per cent. Vertigo, usually of moderate intensity, was present in thirty-six. In three it was severe enough to justify lumbar puncture, and in each case an abnormal spinal fluid was found. In one case the vertigo was so severe that a diagnosis of tumor at the cerebello-potine angle had been made, and operation contemplated. Futher study disclosed a low basal rate which directed attention to the thyroid, and other tests confirmed the diagnosis of hypothyroidism. The patient has now been under treatment for two years. He had only one attack of vertigo after treatment was instituted, and has had no vertigo at all during the past twelve months. No myxedema was demonstrable in this patient. The cause of the vertigo in hypothyroidism is not established, but two explanations offer themselves. The most obvious, and perhaps the simplest would be to ascribe it to cerebral anaemia, due to the slow pulse and low blood pressure characteristic of the underlying condition. This may well be the cause of the milder types of vertigo, which, by the majority of our patients were described as transient, and associated with rapid changes in posture. It would hardly explain, however, the severe attacks to which the patient mentioned above was subject, and which have also been recently described by Moehlig (34). It seems much more likely that the cause of such severe vertigo, which closely simulates Meniere's syndrome, lies in the abnormal spinal fluid which is found in severe cases of thyroid failure. Our findings in three cases have been paralleled by Ayer (personal communication) in a similar but slightly larger group, and indicate a marked departure from normal, as shown

by pressure changes, the nitrogen fractions, and the gold sol curve. Further study is necessary to establish the relation of these findings to the vertigo, but the fact that Ayer has demonstrated that the fluid returns to normal under thyroid treatment makes it clear that the abnormalities are but one more manifestation of the far reaching effect of thyroid failure upon bodily function.

Deafness of the progressive, non-catarrhal type occurred in 15 per cent of our patients; in 7 per cent it was accompanied by tinnitus. This association of deafness and thyroid failure was pointed out by Falta (8), who ascribed the impairment of hearing to myxedemic changes in the eighth nerve. In most of our patients, however, no myxedema was demonstrable, and it seems more probable that the diminished hearing depends upon nutritional changes due to the thyroid failure. Whatever the local change may be, the fact that the hearing improves when the metabolism is normalized with thyroid extract leaves no doubt that the deafness is dependent, in part if not entirely, upon the thyroid hypofunction. The entire subject of progressive non-catarrhal deafness demands restudy, and two of its outstanding characteristics, *i. e.*, inheritance and exacerbation after pregnancy, indicate clearly the necessity of including examination of vital functions in such a study.

Parasthesias are common in hypothyroidism and often severe. Usually they consist of numbness and tingling. One of our patients was unable to continue her work as a cook because her fingers had become so numb that she could not handle dishes without dropping them. In another the tongue was affected, causing thick, unintelligible speech. The most common site of the parasthesias is, however, the extremities, which are often described as feeling as though they were wrapped in cotton wool. The immediate cause of these disturbances of sensation is not clear. They may be due either to nutritional changes in the nerve trunks, or to the pathological cerebro-spinal fluid. They disappear promptly under treatment.

Digestive System: Constipation and variable or diminished appetite are the outstanding digestive symptoms in this as in other series. The latter is usually ascribed to the former, but it

seems possible that other factors may be operative. These will be considered below. The constipation is of the atonic type, is aggravated by a diet rich in roughage, and is resistant to treatment by cathartics. It responds readily to thyroid extract.

Biliary Tract: Because of the prominence of vomiting, indigestion, and jaundice in our patients (see Table XIV) it seemed worthwhile to study the digestive tract by means of barium meals and radiography, Graham test, and duodenal lavage in a number of cases. The results of this investigation appear in Table XV.

TABLE XV

RELATIVE INCIDENCE OF LIVER AND GALL BLADDER DISEASE

Diagnostic Evidence	Thyroid	Not Endocrine		Pituitary
		Long Form	Short Form	
		Established		
Liver Function				
+	7	12	2	4
++	7	9	1	3
+++	8	7	5	0
Graham	1	4	2	1
Operation	2	0	0	0
Jaundice (current)	1	0	0	0
Total	26	32	10	8
		Probable		
History				
Previous jaundice	5	3	1	0
Miscellaneous	3	0	2	0
Physical Examination				
Enlarged liver	2	1	0	0
Tenderness	3	0	0	0
Miscellaneous Findings	0	0	2*	0
Total	13	4	5	0
Grand total	39	36	15	8

Comparison has been made between four series of one hundred consecutive cases each, exhibiting respectively thyroid and pituitary disease, and non-endocrine disorders as determined by

*One case of profound secondary anaemia without determined cause, one case showing duodenal pathology by radiography.

the "Long Form" and "Short Form" studies. The choice of the two latter depends upon the fact that because of certain studies now under way many cases are received selectively for the longer investigation in which a liver (or gall bladder) element is patent before admission. The "Short Form" group is much more representatively a cross section of the general endocrine service. Positive evidences of involvement of liver, gall bladder or both derive from the duodenal function test (McClure), positive Graham test, history of recent cholecystectomy or current jaundice. The probable evidences lie in the facts of the past history, the results of physical examination or other suggestive observations. While but single defining evidences are reported in the table, it is to be understood that the thorough general study adds numerous supporting observations. For example, a number of the positive liver function cases gave positive Graham tests, icteric indices, etc., as well as yet other positive indications.* Reverting to the table, it is patent that liver or gall bladder disease is from three to five times as common in thyroid as in pituitary disease, and more than twice as frequent as in a typical group of non-endocrine complaints. The relative parity of incidence in the "Long Form" series of non-endocrine disorders derives in part, as noted above, from the fact that this group selectively contains a number of liver cases admitted for that study.

Biliary Function: From the tabulation it is apparent that disturbance of biliary function frequently complicates hypothyroidism. This is of possible importance in explaining the apparently conflicting findings in regard to sugar tolerance in certain patients. If the sugar tolerance suggests disturbed pituitary function, and all other findings are more consistent with hypothyroidism, determination of the biliary function by appropriate methods will often eliminate the apparent conflict.

Whether or not hypothyroidism and disturbances of the biliary tract are causally interrelated, we cannot state from the evidence at hand. It may be, however, that a diseased gall

*It may not be inapposite here to state that in our opinion, the duodenal function test gives primary information about the level of liver function, while the Graham test, naturally, deals with the gall bladder. With a positive Graham, the function test is usually positive also, but a negative Graham test frequently occurs with a positive liver function test. An inference tentatively offered and awaiting confirmation by further study is that gall bladder disease is usually associated with liver dysfunction, but that the converse is by no means of as frequent occurrence.

bladder furnishes the focus of infection which is the etiological factor in the depression of thyroid function in a given case, and it also seems possible that sluggish biliary function due to thyroid failure may prepare the way for various liver disturbances. The question is being intensively studied in the Clinic, and final conclusions will be reported when sufficient material is available.

Reproductive System: A prominent symptom in our patients was disturbance of menstrual function, not dependent on pelvic disease. The type of disturbance was characteristic. Complete amenorrhea, so common in pituitary hypofunction, was rare. Nor does the gradual lengthening of the intermenstrual interval and diminution of duration and amount of flow, likewise characteristic of that condition, occur so frequently in this series of patients. In hypothyroidism the characteristic menstrual disturbance may be characterized as loss of control. Menorrhagia is more common than diminished flow, and the intermenstrual interval becomes markedly disturbed. It may vary from ten days to three months in any given patient. Pain at onset of menstruation occurred in a few of our patients in whom the periods had never become normally established, but it is so uncommon in hypothyroidism that its presence should always suggest possible pelvic involvement.

Sterility was present in 39 per cent of our married patients. It was not always possible to determine, in this series, whether the responsibility lay with the patient or the mate, but a special investigation of sterility which we are now carrying out confirms our impression that hypothyroidism may be the sole factor in the production of a sterile marriage, if it exists in either male or female. There are in this series examples of both male and female sterility associated with hypothyroidism, and overcome by proper thyroid medication. One male patient had been married three years, no barrier to pregnancy could be demonstrated in his wife, and, except for lack of energy, he considered himself in perfect health. The full protocol is given later. His physical examination showed no myxedema present. His basal rate was —25 per cent. He was put on thyroid extract June 16; his basal metabolism was normal on (or before) August 18. His wife had a normal menstrual period August 5-9, but the next

period was missed and all the normal signs and symptoms of pregnancy developed. She was delivered, at full term, of a normal babe. It is an important fact in this case that the husband showed spermatozoa of normal number and motility in the condom specimen, and that many of them were dead in the post-coital specimen. Apparently the sterility was due to low vitality of the spermatozoa, which could not survive long enough to meet and penetrate the ovum. As a corollary, a normal condom specimen cannot be accepted as positive proof of potency in the male.

In the females, sterility was as a rule due to failure of conception, and was characteristically accompanied by diminished libido. In one patient this amounted to absolute frigidity, although she had had before the onset of the hypothyroidism normal libido and fertility. In certain cases, however, the sterility is due to repeated miscarriage. An example of this is found in one patient in the series who, after the birth of her first baby, had a severe streptococcus infection of the throat. Thereafter she became easily fatigable and felt "generally below par." She became pregnant three times, but in each instance miscarried without known cause at the end of the third month. Physical examination showed some evidences of malnutrition, low blood pressure, sub-normal temperature, and slow pulse. Her basal rate was —22 per cent. She was given thyroid extract in amounts sufficient to normalize the basal rate. She is now eight months pregnant, and no miscarriage has threatened.

It seems fair to postulate that normal thyroid function in both partners is necessary for a fertile mating. Various explanations of the manner in which thyroid failure operates to destroy fertility have been advanced, most of them involving some subtle and specific interrelation between thyroid and gonad function. Such a theory seems to us unnecessarily complicated and lacking in proof. Sterility, diminished libido and menstrual disturbances are common symptoms of any disease which seriously interferes with bodily nutrition, and we believe that it is by reason of such interference that thyroid hypofunction operates to produce the symptoms referable to the reproductive organs.

Impotence: Among our male patients impotence, relieved by thyroid medication, was present in three instances. It is

hard to get accurate information about this symptom, and it is probably more common than our figures indicate. Like sterility, it is simply one evidence of the malnutrition due to the disturbed thyroid function. Its importance lies in the fact that the impotence is generally ascribed to gonad failure, in the absence of other demonstrable cause, and the patient treated on that basis, with generally disappointing results. In our experience primary gonad failure, especially as a cause for impotence or frigidity, is a much rarer condition than thyroid or pituitary hypofunction.

Skin and Appendages: The value of the skin as an index of nutrition, is too often overlooked in these days of instruments of precision. This is especially true in regard to diseases of metabolism. That the skin is profoundly affected by depression of thyroid activity is indicated by the frequency with which complaints regarding its condition appear in the patients' histories (see Tables XIV and XVI). Dry, cold skin was present in one-half the series, loss of hair in one-third, thickening and scaliness in 10 and 7 per cent, respectively, and skin eruptions, usually eczematous, in 12 per cent. There is, in these patients, a typical pallid, lifeless appearance of the skin, hair and nails which should always suggest to the examiner disturbed metabolism in general and thyroid hypofunction in particular, especially if anæmia be absent or slight. It must be emphasized, however, that these symptoms are suggestive evidence only and demand much corroborative evidence before they can be regarded as diagnostic of hypothyroidism. It is perhaps noteworthy that myxedema was demonstrable in only 10 per cent of our cases, showing how frequently marked depression of thyroid function exists without this so-called pathognomonic symptom.

However suggestive of hypothyroidism the patient's history may be, a careful and complete examination is essential for two reasons. First, it serves to detect or eliminate organic disease as a basis for the symptoms. If organic disease be demonstrable, consideration of endocrine disturbances should be postponed until it has been eliminated or evaluated. Second, a careful physical examination will bring to light certain findings which in connection with the symptoms should establish a suspicion of metabolic disturbance strong enough to demand investigation of the patient's level of functional performance.

General Nutrition: Among the physical findings referred to are the various evidences of malnutrition, such as abnormal weight, either above or below the normal. A reference to Table XVI shows how common these symptoms are in patients with hypothyroidism. Evidence of poor general nutrition was present in 78 per cent of our patients, and the skin was credited with

TABLE XVI

PHYSICAL EXAMINATION

Skeletal development, over	3%
Skeletal development, under	4%
More than 10% overweight	32%
More than 10% underweight	21%
Nutrition, fair	27%
Nutrition, poor	51%
Skin, dry and cold	50%
Skin, dry and scaly	10%
Skin, thick	7%
Skin, myxedematous	10%
Malar flush	18%
Hair, scanty	30%
Hair, hypertrichosis	3%
Hair, coarse and dry	28%
Tonsils, absent	40%
Tonsils, infected	24%
Thyroid, enlarged	21%
Heart, enlarged	4%
Heart, faint sounds	31%
Heart, murmurs	6%
Heart, low voltage (cardiogram)	46%*
Arteriosclerosis	16%
Hypertension	10%
Hypotension, systolic < 100 mm.	26%
Hypotension, diastolic < 60 mm.	12%
Hypotension, total	69%
Pulse rate, above 80	4%†
Pulse rate, below 70	66%†

*Only 13 cases examined in this series.
†In substantial agreement with the larger series.

being normal in only 33 per cent. Dryness was its characteristic departure from health, but thickening, scaling, myxedematous infiltration and eruptions of which eczema was the commonest, were often combined with the dryness. The skin was cold to the touch in half the patients.

Hair: The hair is apparently more resistant to the effects of hypothyroidism than is the skin, as it was judged to be normal in 54 per cent of our series. It was termed "thin" and "scanty" in about one-quarter of the patients; coarse, dry and lifeless in an equal number. Alopecia areata was prominent in one patient, complete alopecia was present in two. Excessive hair growth is a rare finding, in contradistinction to certain of the other endocrine disorders.

Focal Infection: As has been already pointed out, the incidence of absent or infected tonsils is extremely high in our patients, the former condition existing in 40 per cent, the latter in 24 per cent. In only 36 per cent were apparently normal tonsils present. These figures are significant, even in these days of enthusiastic tonsillectomy.

Thyroid Gland: Goitre was present in 21 per cent of our patients. In all, it was apparently due to simple enlargement. The importance of the finding lies in its negative value in ruling out hypofunction of the thyroid. We have seen goiter, tremor and tachycardia all present in a patient with myxedema, existing as residua of a pre-existing thyrotoxicosis.

Heart: Convincing evidence of cardiac enlargement was present in only four of our patients, and in none was the enlargement such as Fahr (35) describes as the typical "myxedema" heart.

Murmurs were also conspicuous by their absence, due not improbably to the lack of muscle tone in many instances. This lack of muscle tone is evidenced by the faintness of the heart sounds in these patients, and by electrocardiographic evidence of low voltage. Faint heart sounds were noted in 31 per cent of our series, low voltage in the electrocardiograms in 46 per cent of those examined. One of us (36) has previously reported the presence of this low voltage in hypothyroidism, and its disappearance under thyroid treatment.

Irregularities: No irregularities other than an occasional premature beat were noted in our series.

Pulse Rate: Bradycardia is so characteristic of hypothyroidism that the presence of the former should always suggest

the latter. Sixty-six per cent of our patients had pulse rates below 70 per minute, while only 30 per cent had normal rates and 4 per cent accelerated rates. In these last, there was evidence of arteriosclerosis and true myocardial insufficiency. The lowest rate recorded in our series was 43 beats per minute. This patient's heart was apparently normal; certainly there was no heart block present.

Arteries: Sclerosis in demonstrable amount was present in 16 per cent of our patients. These included all in whom myxedema was demonstrated. Several of the patients with sclerosis were well below the age at which that condition is usually found.

Blood Pressure: Normal blood pressure existed in 21 per cent of the series. Hypertension was demonstrated in 10 per cent, accompanying arteriosclerosis and myxedema. Hypotension was recorded in 69 per cent of patients. If there be any error in measurements, it is like that of basal metabolism, practically always on the high side, so that our figures do not exaggerate the incidence of hypotension in hypothyroidism. Twenty-six of our patients registered a systolic pressure of less than 100, the minimum being 80, and twelve had a diastolic pressure under 60, the minimum being 45. That the hypotension is due to the thyroid depression is proved by the return of the blood pressure to normal in these patients under proper medication. It is not necessary to drag the adrenals into the picture to explain the hypotension.

The Cardio-Renal System: For many years it has been recognized that the typical myxedemic is prone to show evidences of degenerative changes in heart, blood vessels and kidneys. Our findings in this respect have already been presented and commented upon (33), but it seems necessary to risk repetition in order to make clear our opinion concerning the role played by cardio-renal insufficiency in thyroid hypofunction, and especially in the myxedemic form.

The majority of our patients showed no myxedema, and no definite evidence of cardio-renal disease. In a small fraction, however, myxedema was demonstrable, and in these patients certain evidence of markedly impaired circulatory and renal function, similar to that found in chronic nephritis was present. One

or more of the following findings existed in every case of myxedema: albuminuria, with or without casts; nitrogen retention, as shown by the chemical examination of the blood; arteriosclerosis, hypertension, enlarged heart, or electrocardiographic findings similar to those found in myocardial degeneration. These findings we have grouped under the term "pseudo-nephritis," since they differ from true nephritis in that they are, with the exception of arteriosclerosis, and in some instances hypertension, amenable to treatment with thyroid extract. One of us (33, 37) has already pointed out the close association of this "pseudo-nephritis" with myxedema, and has expressed the belief that the latter is dependent upon the former. Until contemplated animal experimentation has furnished further evidence, we cannot regard the thesis as proven, but we wish here to emphasize the fact that evidences of cardio-renal depression or degeneration are far more common in the myxedemic than in the non-myxedemic group of patients. That the latter group should be regarded as "atypical" is, we believe, due to misconception. The fact that patients in this group are markedly underweight does not argue against this belief, for underweight is well known to exist in the most severe of all thyroid depressions, "cachexia thyropriva." The effect of normal thyroid function upon body weight is to keep it normal; in the absence of such normal thyroid activity the weight may become abnormal by either increasing or decreasing. The factors that determine the direction of its departure from normal are as yet unknown. The myxedemic patient then should be regarded as one in whom circulatory or renal insufficiency, or both, have developed on the basis of a thyroid hypofunction, giving rise to a "pseudo-nephritic" condition, but may have an equally severe depression of thyroid function.

Dysthyroidism is the term which we believe is better applied to atypical cases of thyroid hypofunction, since these patients usually exhibit symptoms of both "hypo-" and "hyper-activity" of the gland. They represent, in our belief, individuals who are examined while a previous over-activity is swinging to the underactive level, which is not infrequently its final stage. During this period of transition, certain symptoms due to the previous "hyperactivity" tend to persist longer than others, so that there

exists an apparently paradoxical situation in which nervousness and tachycardia, for example, coexist with hypometabolism and other definite signs of thyroid hypofunction. Eventually such patients either become normal, or, more often, reach a definitely hypofunctional level. The interest in the condition lies in the fact that it explains some of the apparently contradictory findings in certain cases, and that it raises a question as to the advisability of immediate operation, and its extent, in mild cases of thyrotoxicosis. Our own belief is that in the absence of symptoms of cardiac embarrassment such patients should be kept under close supervision until the transition stage is past, and that the type and extent of treatment necessary can then be logically determined. If such a course is pursued, frequent determinations of the basal rate are essential, since the pulse rate, which falls far more slowly, cannot be relied on to give evidence of diminishing thyroid activity. The trend of weight and blood pressure are also important guides.

From the clinical point of view, there are many objections to regarding the estimation of the basal metabolism as a perfectly reliable method of diagnosis of, and progress in, thyroid disturbances. If it be really the basal metabolic rate which is determined, the importance of the first and subsequent readings can hardly be overestimated, but unless the operator understands thoroughly the many factors which may influence the readings, a true rate will not be obtained. We have seen, in this Clinic, a difference between the initial and final determinations of an untreated patient's basal rate amounting to 107 per cent, and varying from an abnormally high to an abnormally low value, without apparent change in the conditions of the test, and due solely to emotional factors which are often difficult of detection. We believe therefore that the basal metabolic rate alone is not a reliable criterion of thyroid activity, and that in the more obscure cases it must be supplemented by the patient's history, physical examination, and a group of other tests and examinations such as are reported in this paper.

In addition to the type of dysthyroidism described above, there is reported in the protocols below a case representative of a small group showing another class of disturbance. In them the basal rate is not altered to a degree comparable to the evident symptoms of toxicity, but the sugar tolerance, usually only

slightly altered in thyroid disturbances, is markedly affected. The theoretical significance of these findings is discussed below. They are mentioned here to show that the basal metabolic rate cannot safely be accepted as the sole criterion of the level of thyroid function.

PART III—CASE PROTOCOLS

TABLE XVII

	Gall Bladder			Psychoses		
Case Number	B-467	B-480	B-845	B-875	B-528	B-35
Diagnosis	—	—	—	*—	—	—
Sex	M	F	M	F	M	F
Age (yrs.)	31	52	37	32	61	41
Height (cm.)	180	163	173	171	177	165
Weight (kgm.)	58.7	91.2	48.6	80.2	92.4	68.7
Weight Deviation (%)	−25	+45	−33	+32	+26	+15
Lung Volume Deviation (%)	+6	−52	−27	−12	−14	−46
Basal Rate Deviation (%)	−29	−36	−33	−32	−29	−50
Blood Pressure (mm.)	104/60	130/70	116/88	110/70	146/90	104/70
Pulse (per min.)	46	48	56	60	64	71
Temperature (deg. F.)	97.4	98.0	98.6	97.8	97.8	95.4
Alveolar CO_2 (mm.)	41	43	43	43	35	33
Urine Volume (cc.)	600	1290	1120	850	790	990
Spec. Grav.	1.024	1.013	1.020	1.019	1.024	1.010
Albumin	0	+	0	0	0	+
Casts	0	0	0	0	0	0
Sugar	0	0	0	0	+	0
Total Nitrogen (gms.)	8.32	7.57	9.30	5.72	5.50	7.62
Residual Nitrogen (%)	14.5	8.2	6.3	9.0	9.8	6.6
"Urobilinogen"	0	+	0	0	0	0
Phen. Sulph. Phthal. (%)	50	25	51	49	39	33
Galac. Tol. Deviation (%)	−33	−83	±0	−25	±0	+25
Non-Protein Nitrogen (mgm.)	40	29	33	26	29	31
Uric Acid (mgm.)	4.4	2.3	4.4	3.3	3.8	3.7
Sugar (mgm.)	100	77	82	83	81	71
Haemoglobin (%)	95	65	85	95	100	70
Erythrocytes (10^6)	4.93	3.34	4.14	4.81	4.97	4.33
Leucocytes (10^3)	5.40	11.9	4.9	6.95	9.60	5.30
Neutrophiles (%)	54	66	45	52	50	62
Lymphocytes (%)	35	27	46	40	38	25
Eosinophiles (%)	6	2	4	1	2	5
Monocytes (%)	5	5	5	7	9	3
(Basophiles) (%)	—	—	—	—	1	5

THYROID FAILURE WITH GALL BLADDER COMPLICATION

GROUP I

CASE B-480. The patient's chief complaint was of abdominal pain coupled with jaundice. The latter condition was first remarked eighteen months previously and the first attack lasted for about a month, with characteristic stool and urine findings. The jaundice cleared up under medication. Following this, there was a period during which she became very fatiguable and mentally sluggish, with occasional attacks of acute nervous instability. Nearly 20 years before she had been treated for myxedema and from time to time in the interim had had occasional courses of thyroid medication.

Family History: Father and one sister died with symptoms similar to those of the patient.

*See discussion of case.

Past History: She reported only measles at the age of 26, severe pneumonia followed by abscess in the right lung at 43, an injury to the spine at 37 which caused temporary paralysis of the left leg. She matured at the age of 9 and had apparently passed through the menopause a few months before admittance. The menstrual history was normal except for menorrhagia prior to the cessation of the periods. She had been married twice, her first experience lasted 3½ years, with three pregnancies, resulting in one surviving child, a miscarriage at three and a half months, and a child who died at birth. Her second marriage produced one miscarriage four years previously, resulting from a fall while three months pregnant. She had always been constipated; had had a tendency to obesity at times, checked by drastic dietary.

Physical Examination: The patient was deeply jaundiced, obese woman, 52 years of age, apparently asthenic and showing a marked mental sluggishness. The scleræ were deeply jaundiced, the few remaining teeth were in poor condition, tonsils were enlarged and cryptic, and there was a slight thyroid enlargement. There was a tenderness on palpation over the entire abdomen, more pronounced over the liver, which was somewhat enlarged; the pubic hair was scanty, skin coarse, dry and deeply pigmented, and large fat deposits were observed on the breast and abdomen. The abdominal reflexes were reported as absent.

Laboratory Summary: The patient was 45 per cent above her predicted weight, while the lung volume was less than half that of prediction. She had a basal rate of —36 per cent, with marked bradycardia and substantially normal blood pressure. The urine showed albumin and bile, also a positive "urobilinogen" test. Phthalein elimination was but 25 per cent. The patient's sugar tolerance was greatly lowered. Blood sugar was slightly below normal. Her blood showed a definite secondary anæmia, a slight leucocytosis, and a substantially normal formula.

Pelvic Examination showed residua of early child-bearing; a large fundus was freely movable and in good position; the findings were otherwise normal.

The sella by *radiography* was normal; the lower teeth showed absorption.

Eye Examination showed contraction of the form and color fields too marked to permit the delineation of the blind spots.*

Neurological Examination disclosed evidence of multiple neuritis and emotional instability.

Laryngological Examination showed hypertrophied and infected tonsils.

An earlier gastro-intestinal radiographic study had demonstrated a cholecystitis.

Diagnosis: The patient's condition was obviously thyroid failure coupled with gall bladder disease and a probable dysfunction of the liver. There was also a definite psychoneurosis.

Comment: Operation for the gall bladder condition was recommended, to be accompanied and followed by controlled thyroid medication. The operation was successful, a grossly diseased gall bladder being removed. Her jaundice cleared rapidly and she was discharged to continue her thyroid medication. Some two years later she returned

*Fields of this type have been recorded by one of us in a number of cases of gall bladder and liver disease. Unpublished data, A. W. R.

to the clinic in a much improved condition. Her thyroid medication had been somewhat intermittent and she had increased in weight to 68 per cent above prediction. A duodenal study showed considerable disturbance of biliary function of the liver, a residuum of the earlier gall bladder condition. Her earlier low sugar tolerance had increased to the normal. The eye grounds were still further contracted. Under controlled thyroid medication for a few weeks her basal rate was brought promptly to a normal level. The nervous instability of which she had earlier complained had returned, but a number of social factors had appeared which were undoubtedly of definite significance in producing this result. In spite of this, the mental picture was greatly improved.

CASE B-467. The patient's chief complaint was of "bilious attacks," from which he had suffered since childhood. They were characterized by constipation, acid eructation, drowsiness, and dull headaches following meals. There was also a mental dullness of which the patient was acutely conscious, and periods of mental depression. He had attempted to correct the condition by dieting and had eliminated a number of articles of food which he believed to be badly tolerated. Investigation showed that his remaining dietary regimen was entirely inadequate, although containing a maintenance quantity of protein. There has been a gradual loss of weight and a general physical depression.

Family History: The father was reported as having had a liver trouble of unknown character and possibly exophthalmic goiter.

Past History: The patient was born in South Africa and lived there until the age of 19. He had lived in England since that time, except for two years in the army in France and in the Salonika campaign. He reported most of the minor ailments of childhood, malaria in 1916 with jaundice, and several brief recurrences of this condition until an attack of rheumatic fever in 1917. He had had no malaria since this latter condition, but had had two attacks of jaundice in 1925. He had been subject to asthma since the age of 9, also bronchitis; he had an attack of influenza at the time of the epidemic. He reported a possible protein sensitivity to horse dandruff and to feathers. His appetite was good, but digestion was poor. Among other interdicted articles of food were eggs, cheese, and fats of all kinds. He had used Epsom salts and calomel very freely.

Physical Examination showed a very well set up and athletic, but undernourished, Englishman of 31 years of age. There was a yellowish tinge to the skin and the conjunctivæ were yellowish. His abundant black hair was tinged with gray; the teeth showed much dentistry; there was some minor adenopathy in the neck. The heart was normal and there was no tenderness over the gall bladder. The left testicle was undescended. The thyroid was not enlarged. The remaining findings were substantially normal.

Laboratory Summary: The patient was 25 per cent under his predicted weight, showed a basal rate of —29 per cent, with low blood pressure, bradycardia, and somewhat subnormal temperature. The scanty urine was free from abnormalities except a high residual nitrogen. The sugar tolerance was somewhat depressed. The blood chemistry gave evidence of some retention. The blood morphology showed a lymphoid blood with a slight eosinophilia, undoubtedly due to his protein sensitivity.

Repeated examination of the blood for plasmodia failed to show them.

Neurological findings were normal.

Abdominal findings were normal.

Endermal Tests: A positive response to egg and doubtful positive to wheat and milk was found; the reaction was negative to a large number of other proteins.

Radiography: A gastro-intestinal series was substantially normal. The skull and sinuses were normal. The chest showed increased density at the right apex, with haziness and scattered mottling over the whole lung area. A Graham test by the oral route was negative.

Duodenal Function Test (McClure): The patient showed a very marked disturbance of biliary function.

Audiogram: Substantially normal hearing was found.

Stool Examination: Blood, ova, parasites, and cysts were reported absent.

Cardiac Examination: Beyond a short systolic murmur, with the first sound at the apex, a frequent finding in normal individuals, the findings were entirely normal.

Eye Examination: Gave normal findings.

Discussion: On the basis of the findings given, a diagnosis of hypothyroidism, coupled with a liver dysfunction, was established. Thyroid medication was suggested for the first, and duodenal lavage for the second. Under this treatment the patient's condition rapidly cleared; he gained in weight, the jaundice disappeared, sugar tolerance became normal, and the general laboratory picture showed marked improvement, including a disappearance of the blood chemistry findings suggesting lowered kidney permeability (see pseudonephritis later). Shortly after this study the patient returned to England, and we are advised that he has had one or two relapses of the liver condition, which, however, have yielded to further treatment by lavage.

CASE B-845. The patient's chief complaint was of skin eruption and an inability to digest certain foods. In 1909 he developed a skin disease diagnosed as ichthyosis. The skin became hypertrophic; there was much exfoliation, with a transitory and recurrent erythema. The latter seemed to depend primarily on the use of such foods as fat, fruit, and milk. Milk caused abdominal pain, while fats have produced a yellow color of the skin. High protein diet will also cause the yellow color, but the patient could take liver freely, an interesting point in view of his fat intolerance.

Family History: Two grandparents died of cancer, and the mother had been operated upon for gall stones.

Past History: The patient reported the minor ailments of childhood, together with pneumonia and diphtheria in early years. Influenza at the time of the epidemic was complicated by an involvement of the antra and ethmoids, which later disappeared without treatment. An appendectomy was performed in 1909, and an exploratory laparotomy in 1917 showed an alleged normal gall bladder. The patient had also been operated upon for tonsilitis, hemorrhoids, and had had several infected teeth extracted. He complained of an occasional unilateral headache, marked optic fatigue, occasional pain in the right ear. and recurrent pharyngitis after the use of milk or cream. Recently he had had attacks of precordial pain, which was aggravated

by the use of thyroid. Tingling and numbness of the hands and feet and some myalgia had been recent developments. For some time past he had had a non-specific prostatitis. He had lost 17 pounds in the six months prior to his admission.

Physical Examination: The patient was a well-developed but distinctly emaciated white man, 37 years of age; the face was pallid with a definite lemon-yellow cast; the conjunctivæ were slightly yellowish. There was a moderate deviation of the septum. No thyroid enlargement was present. The heart sounds were indistinct, the beat irregular, with recurrence of several rapid beats which were not typical extrasystoles. There was definite bradycardia and hypotensive blood pressure. The right testicle was somewhat tender and there was possibly tenderness over the gall bladder. Minor inguinal and definite cervical adenopathy was found. The skin was dry, scaly, and hypertrophic. The tendon reflexes were reported as sluggish.

Laboratory Summary: The patient was 33 per cent below his predicted weight, the lung volume but slightly below prediction. The basal rate was —33 per cent. The blood pressure recorded at this time was distinctly higher than upon several other observations, but still hypotensive. There was bradycardia. The sugar tolerance was normal; the blood uric acid high. There was a slight secondary anæmia and borderline leukopenia. The blood was lymphoid in type, with a slight relative increase in the eosinophiles.

Skin Examination: There was a mild ichthyosis, suggestive of thyroid failure. Several other possibilities were considered and rejected on the ground of other observations.

Endermal Tests: The patient reacted positively to several cereals —celery, spinach and peas—and negatively to a large number of common food proteins.

Cardiac Examination gave entirely normal findings. The cardiogram showed a slurring of the QRS complex and the contour of the "T" wave in leads II and III was suggestive of possible myocardial impairment, without defining it.

Neurological Examination gave substantially normal findings, except for a possible loss in deep sensation over the lower extremities and somewhat diminished reflexes.

Abdominal Examination disclosed no abnormalities, failing to confirm the earlier report of tenderness over the gall bladder.

Eye Examination showed normal conditions.

Radiography of heart, lungs, diaphragm, lumbar spine, hips, pelvis, and skull disclosed no abnormalities.

Neutral Red Test: Normal.

Gastric Examination: Abundant free hydrochloric acid.

Endoscopic Examination showed an enlarged, tender prostate, with involved left seminal vessels and normal bladder.

Duodenal Function Test showed marked hepatic disturbance.

Icteric Index: 50-75.

Van den Bergh: Negative.

Pancreatic Enzyme Examination showed normal concentration and activity.

Laryngological Examination gave normal findings.

Microscopic Examination: Numerous giardia were demonstrated in the duodenal contents.

Discussion: The case presented a number of interesting possibilities. Primary anæmia was ruled out by the tests given above and by repeated examinations of the blood, none of which gave any indication of this condition. The normal pancreatic lipase content referred the patient's fat intolerance to the biliary disturbance. The demonstration of the giardias in the duodenal contents (a fact of which the patient had been earlier advised) offered a basis for the patent disturbance of gall bladder and presumptively liver function. In addition there was a definite thyroid failure. It was felt in this case that the invasion of the duodenum by the parasite was probably a starting point for the general condition. Duodenal lavage with substances such as magnesium sulphate, known to be antagonistic to these parasites, was advised. Thyroid medication was also recommended, recognizing, on the basis of past experience that complete correction could be expected only when the parasites had been exterminated and the liver brought back to a normal level of functional activity. Later advices showed some improvement in the condition, but the giardia are still present.

GROUP II. PSYCHOSES

CASE B-35. The patient's chief complaint was easy fatigability, with lameness in the left knee and general nervousness. The entire picture was dated from the birth of the patient's last child in 1918, five years before the patient was seen. Several earlier medical contacts had ascribed the patient's condition to pelvic disorders and an operation had been advised, which had been refused, however. The patient was in a markedly depressed condition, from which she would emerge into sudden bursts of temper without exciting cause. There were several halucinations, the whole defining a manic depressive psychosis.

Family History was not significant.

Past History: The patient reported the minor ailments, scarlet fever and pneumonia in childhood and typhoid fever at the age of 26. A tonsillectomy had been done the year before. She had been subject to head-colds. Her bowels were constipated. Otherwise the history was not remarkable. She had been married for 12 years and had borne three children without miscarriage. The menstrual history was not remarkable beyond brief and somewhat scanty periods.

Physical Examination: The patient was a well-developed, somewhat obese white woman, 41 years of age. The skin was very dry and scaly, hypertrophic, and did not pit on pressure. The hair of the head and eyebrows was coarse and somewhat scanty. The palpebral fissures were narrow, the upper and lower eyelids were puffy, the tongue increased in size, but without tremor on extension and not prominently fissured. A few bubbling rales were reported in the region of the bronchi; blood pressure was low, and there was definite bradycardia; the hands were broad, fingers short, the nails were thickened and striated; the facies was typical of myxedema. The patient's mental reaction was very sluggish and the speech thick, possibly as the result of enlarged tongue.

Laboratory Summary: The patient was overweight and nearly 50 per cent below predicted lung volume. The basal rate was —50

per cent, the blood pressure low, the pulse normally very slow, though at the time of the reported basal examination it was 71. There was a marked subnormal temperature. The low alveolar carbon dioxide was probably due to the patient's inability to cooperate. The sugar tolerance was slightly increased. Blood sugar was low, and the blood morphology showed a secondary anæmia with a 5 per cent basophilia. An interesting point in connection with this case is recorded in a basal test done during the latter part of the patient's stay. At this time she had developed a slight infection and showed a temperature of 100.8° F. The basal rate at this time was —25 per cent. If we calculated to her usual daily temperature this would correspond to a value around —60 per cent. Another interesting point was found in a series of comparative blood pressure measurements. The first recorded, at a time when the patient was in a tense, nervous condition, was 166/110. Subsequent measurements made under quiet conditions showed an average slightly below that recorded in the table.

Eye Examination: The patient showed substantially normal findings, except for slightly enlarged blind spots and cutting of the upper form fields, due to lid droop.

X-Ray: Chest and skull were normal.

Pelvic Examination gave normal findings.

Neurological Examination: There was no evidence of organic nervous lesion. The patient's mental state was ascribed to her glandular condition.

Discussion: The presenting data warranted the diagnosis of marked hypothyroidism with myxedema. Thyroid medication was recommended, and this was actively carried out. In the course of a few months the patient showed the usual remarkable results which may be confidently expected from controlled thyroid medication in an uncomplicated case of thyroid failure. A most interesting feature of the case was the complete disappearance of the mental symptoms, which at the end of five years have shown no tendency to return.

CASE B-528. The patient's chief complaint was of a recurrent profound mental depression, of which this was the latest attack, the first having appeared some 23 years before. Three years later there was a recurrence which cleared up spontaneously in a few months, and again 14 years later there was a three months' attack. In the preceding year there had been a downward tendency, but the progress had been so slow that it did not become serious until a short time before admission. The last attack had been characterized by an attempt at suicide, the earlier seizures having shown no tendency toward self-destruction.

Family History: Beyond a sister with epilepsy, the history was not informative.

Past History: The patient reported the usual minor ailments with freedom from any serious disease. He had a slight productive cough apparently arising in a throat irritation. The bowels were regular. There was a question of jaundice many years before. He had been overweight for a number of years.

Physical Examination: The patient was a well-developed, obese man of 61 in a state of marked mental depression. His complexion was ruddy, his skin was normal in texture and moisture, the breath was foul. Several teeth were missing and the remainder in only fair condition. The heart and lungs were apparently normal; the

abdomen obese and not tender on palpation; the knee jerks were not elicited.

Laboratory Summary: The patient was 26 per cent overweight; he showed a basal rate of —29 per cent; the urine volume somewhat low; the urine contained a trace of sugar. The protein intake was below a maintenance level; the residual nitrogen high. Sugar tolerance was normal. Blood morphology showed a lymphoid type.

Radiography: The sella was small; teeth were normal.

Cardiogram: Normal.

Neurological Examination gave no evidence of organic nerve lesion.

Eye Examination disclosed slight irregularity of pupils with yellowish discs and some cutting of the upper form fields due to lip droop.

Psychiatric Examination defined a manic depressive psychosis in the depressed phase.

Discussion: Beyond the trace of sugar in the urine, which is occasionally observed in uncomplicated mental cases, and which in the present instance is balanced by the normal galactose tolerance, the presenting picture is one of hypothyroidism. Another possible explanation of the sugar anomaly might lie in the record of an earlier jaundice, but this was so many years ago as probably to be devoid of meaning. Thyroid medication was advised and given with apparently complete recovery on the part of the patient. There has been no subsequent evidence of recurrence in the years that have supervened. Too much weight should not be laid on the correction of the mental condition, but it is interesting to note that the normalizing of the physical state coincided with that of the mental. It may, however, be no more than a coincident remission.

CASE B-875. The patient's chief complaint was fatigability. She had suffered from a manic depressive psychosis for a number of years. Her childhood home conditions were unhappy but she evidenced no marked depression until 10 years ago when she divorced her first husband after one year of married life. For the next two years she showed periods of depression in the fall and winter, followed by terms of exaltation in the remaining two seasons. She attempted suicide in 1919 but voluntarily gave up her attempt out of consideration for her family. She was married again 2 years later, an event which involved a marked change of residence. Has had recurrent periods of depression, during one of which she again attempted suicide. She had received a variety of endocrine therapy without result. Her second attempt at suicide followed a three weeks' course of thyroid medication.

Family History: Her maternal grandfather committed suicide. The history is otherwise irrelevant.

Past History: She had minor ailments, diphtheria and scarlet fever in childhood, jaundice at the age of 7, frequent attacks of tonsilitis and quinsy sore-throat until a tonsil and adenoid operation at the age of 10, which was repeated 12 years later. She has occasional headaches, some tinnitus, and is usually constipated. Her menstrual history shows early onset, marked irregularity, and normal periods. A few years previously she was markedly obese and is still much overweight. She usually loses weight during depressed periods. She has had no children by either marriage.

Physical Examination: The patient is a well-developed, obese woman 32 years of age. The hair is fine and abundant and of normal distribution; there is some nasal obstruction; the thyroid is not enlarged; the heart and lungs are normal; she has somewhat low pulse and blood pressure; the remaining findings are normal.

Laboratory Summary: The patient is distinctly overweight. Her basal rate is -32 per cent, blood pressure and pulse somewhat low. There is a slight oliguria, somewhat high residual nitrogen, inadequate protein intake, and slightly low phthalein output. The sugar tolerance is slightly depressed. Blood sugar is a low normal. The blood is lymphoid in type.

Pelvic Examination: Normal.

Orthopedic Examination: The patient shows poor posture; otherwise is substantially normal.

Radiography shows prominent clinoids, but no other abnormalities.

Cardiogram: Normal.

Eye Examination shows yellowish discs, slightly enlarged blind spots.

TABLE XVIII

	Thin Without Myxedema		Sterility		Deafness	
Case Number	B-44	S-235	S-1013	S-1528	S-407	S-1466
Diagnosis	–	–	–	–	–	±
Sex	F	F	F	M	M	F
Age (yrs.)	41	49	26	34	40	19
Height (cm.)	170	167	160	178	163.5	161.5
Weight (kgm.)	47.8	66.0	83.2	80.9	60.2	63.0
Weight Deviation (%)	−29	−8	+34	+11	+18	±0
Lung Volume Deviation (%)	+6	−32	−12	−3	−6	−10
Basal Rate Deviation (%)	−32	−34	−26	−26	−22	*−12
Blood Pressure (mm.)	108/90	105/58	102/64	106/68	132/80	110/70
Pulse Rate (per min.)	64	54	52	56	72	76
Temperature (deg. F.)	97.6	97.2	97.8	97.1	98.9	98.0
Alveolar CO_2 (mm.)	34	34	43	39	38	43
Urine Volume (cc.)	1420	1280	940	1350	1510	760
Spec. Grav.	1.013	1.019	1.025	1.023	1.015	1.029
Albumin	0	0	0	0	0	0
Casts	0	0	0	0	0	0
Sugar	0	0	+?	0	0	0
Total Nitrogen (gms.)	8.68	10.79	10.70	12.00	9.63	10.94
Residual Nitrogen (%)	5.4	20.4	11.8	10.0	13.6	11.5
"Urobilinogen"	0	0	0	0	0	0
Phen. Sulph. Phthal. (%)	51	35	58	69	45	35
Galac. Tol. Deviation (%)	±0	±0	–	±0	–	−25
Non-Protein Nitrogen (mgm.)	42	29	32	30	25	32
Uric Acid (mgm.)	3.8	2.7	2.8	3.6	3.2	3.0
Sugar (mgm.)	87	105	100	96	100	93
Haemoglobin (%)	85	95	85	100	90	90
Erythrocytes (10^6)	4.36	4.86	4.37	4.95	5.46	5.36
Leucocytes (10^3)	6.80	5.70	7.80	5.20	8.20	8.50
Neutrophiles (%)	39	41	61	50	61	60
Lymphocytes (%)	55	50	36	41	34	28
Eosinophiles (%)	2	3	1	2	0	0
Monocytes (%)	2	5	2	7	5	10
Basophiles (%)	2	1	–	–	0	2

*Transition level.

Psychiatric Examination confirms the diagnosis of a manic depressive psychosis, in the depressed phase.

Discussion: Again barring the slightly lowered sugar tolerance, the picture is one of uncomplicated thyroid failure. The patient's

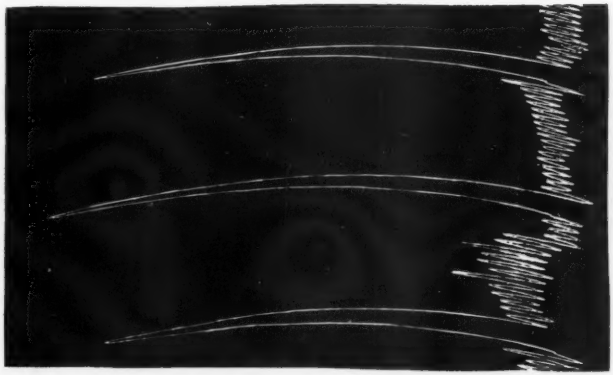
history of an earlier attack of jaundice might offer a possible explanation of the sugar anomaly or, as noted above, it may be intrinsic in the mental condition, as we have observed it in a number of such cases which offered no other explanation for the abnormality. This case is still under treatment and the outcome has not been determined.

GROUP III. AMYXEDEMIC THYROID FAILURE

CASE B-44. The patient's chief complaint was of very severe headaches from which she had suffered since childhood. She usually woke up with them in the early morning. They were completely prostrating, lasted about a day, might come at regular intervals of two or three weeks and again she might be free for two or three months. They were not accompanied by disturbances of vision, but she was often nauseated. A mild glycosuria had been observed on several occasions and the patient found that the headaches were less severe and frequent when under a dietary modification which rendered her sugar free.

Family History: Both the father and one sister had similar headaches.

PLATE 1



Past History: She reported the minor ailments of childhood, one attack of jaundice, severe tonsillitis, and several accidents not relevant to the present difficulty. She had been underweight for a long time. She developed transitory arthritis with urticaria after a serum injection a year previously. She complained of dyspnoea, of palpitation, and occasionally precordial pain. The respiration rate showed a peculiar anomaly with a deep sighing breath at fairly regular intervals. (See Plate I.) The patient was conscious of this and found it extremely embarrassing. The menstrual history shows a normal onset, regularity with a shortened interval and somewhat profuse flow. She had had intermittent attacks of urinary frequency.

Physical Examination: The patient was a poorly developed and nourished woman 41 years of age, with skin smooth and moist. thyroid not enlarged, breasts atrophic, heart and lungs negative, hypo-

tensive blood pressure. The routine neurological examination disclosed only exaggerated knee jerks.

Laboratory Summary: The patient was much below her predicted weight. The basal rate was —32 per cent with low blood pressure, somewhat slow pulse and slightly sub-normal temperature. The basal rate as recorded was undoubtedly too high as the patient was slightly restless. That recorded is the lowest of several observations, all of which, however, were below —20 per cent. Alveolar CO_2 was slightly low but this was probably due to an inability to exhale properly. The urine was normal; nitrogen partition, normal; phthalein test a low borderline normal; sugar tolerance was normal. The blood nitrogen was slightly high; the morphology showed a slight secondary anemia and a lymphoid blood. A provocative urea curve was somewhat low, offering another evidence of lowered kidney permeability.

Barany Test: Normal.

Discussion: While the patient violated most of the conventional clinical signs of hypothyroidism, the essential features of the laboratory picture could be interpreted only in terms of thyroid failure. She was placed on thyroid extract and in a short time showed a complete clinical cure. Her only relapse of significance during the past 5 years was on one occasion when she went for a number of weeks without medication. Resumption of her medicine produced an immediate correction. A short time after treatment was started a brief check-up examination was made. The patient had gained considerably in weight (this is a constant finding in this type of thyroid failure, the patients being initially underweight). The blood pressure had increased to 120/80, the temperature to 98.6°. the basal rate was normal. The phthalein output showed a definite increase. Non-protein nitrogen of the blood had fallen to 30 mgm., while the uric acid had fallen off a few tenths. All the earlier evidences of lowered kidney permeability had practically disappeared. The blood morphology had improved. the lymphocytes having fallen to 37 per cent. This was one of the early cases of what we have designated a "pseudo-nephritis," on which comment has been made earlier in the paper.

CASE S-235. The patient's chief complaint was of fatigability which apparently began in childhood. At the age of 11 she began to put on weight. localized chiefly in the legs. This condition had been a serious annoyance and she had made numerous efforts to correct it but without success. The patient had a wide variety of medical contacts, and had been under intermittent glandular therapy with pituitary extract predominating. Four years before she had developed urinary frequency which was ascribed to cystitis. Two years prior to admission she had had an intestinal stasis demonstrated by the radiography. A radical diet with some glandular therapy had produced some subjective improvement. The bowels were markedly sluggish. There was a loss of hair and dry, rough skin. An inhibiting feature was a feeling of mental depression which the patient was not able to combat.

Family History: Was irrelevant except for the fact that her relatives were all tall, large people.

Past History: She was never strong. She had the usual children's diseases; frequent sore-throats: from 7 until 15 much trouble with running ears. During her school years she found it difficult to concentrate. A tonsillectomy at 30 produced some benefit in the general condition. The catamenial and marital history were negative.

Physical Examination: The patient was a fairly developed, poorly nourished woman of 49. The hair was dry and short, the skin dry and rough, the thyroid was not palpable, the blood pressure was hypotensive. The legs were disproportionately large but not edematous. The remaining findings were substantially normal.

Laboratory Summary: The patient was 8 per cent underweight, and definitely below predicted lung volume. The basal rate was —34 per cent, with low blood pressure, bradycardia, and sub-normal temperature. The urine was normal except for a very high residual nitrogen. The phthalein output was definitely below normal. The low alveolar CO_2 was probably apparent rather than real. The sugar tolerance was normal. The blood showed a marked lymphocytosis.

Neurological Examination showed no abnormalities.

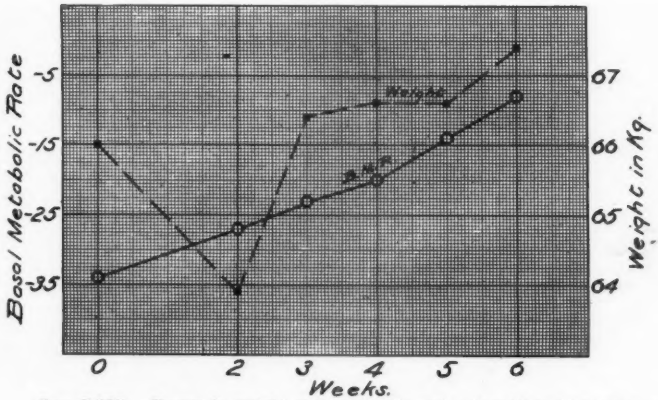
Barany Test: Normal.

Eye Examination showed slightly enlarged blind spots.

Radiography showed a normal sella.

Discussion: That the patient presented an endocrine disorder was patent from the facts as obtained. Further, a thyroid failure was the only endocrinopathy in harmony with the data. Thyroid medication was advised, and through the complete cooperation of the patient it was possible to check the progress of the case over a period of six weeks. Certain significant results are given in the accompanying graph. (See Plate II.)

PLATE II



Case S-235. Change in weight and basal rate under thyroid medication in a case of failure.

It will be noted that there was a loss of weight during the first two-week period which promptly recovered, and the patient showed a net gain of 1.4 kgm. in the six weeks' interval. Later observation had shown a re-distribution of weight, the obesity of the legs having become definitely less.

GROUP IV. STERILITY.

CASE S-1013. The patient's chief complaint was of sterility, coupled with dysmenorrhea. She had been married for two years without becoming pregnant and without at any time having practiced

contraception. She matured at 11, and the history gave regular periods of somewhat brief duration with scanty flow. There had always been pain, appearing shortly after the flow began and lasting about two days. Numerous clots were passed. She had tried various forms of medication, including ovarian extract, without betterment.

Family History: Several cases of malignant neoplasm were recorded; the remaining history was irrelevant.

Past History: The patient reported only measles and whooping cough of the minor ailments and none of the more severe conditions. There was a history at the age of 6 of a fall with trauma to the head, which left no apparent after-effects. Two curettage operations had been performed and fifteen months before her hospital entry one fallopian tube had been taken out. The remaining history shows some intermittent gastro-intestinal disturbances, constipation, and a gain of some 20 lbs. within the past two years. She began to become obese at the time of the onset of the catamenia but had been able to control it in some measure by diet.

Physical Examination: The patient was a well-developed woman, 26 years old, exhibiting a generally distributed obesity. There was a symmetrical thyroid enlargement of moderate amount, a slight tenderness over McBurney's point, and certain postural defects, probably ascribable to obesity. The findings were otherwise normal.

Laboratory Summary: The patient was 34 per cent above her predicted weight. The basal rate, under fairly satisfactory conditions, was 26 per cent below prediction, the lung volume was but slightly impaired, the blood pressure was low with bradycardia. The urine volume was somewhat low with a questionable positive test for sugar. The residual nitrogen fraction was distinctly above the normal; the blood was lymphoid in type.

Radiography showed a normal skull.

Pelvic Examination gave no evidence of pathology.

Discussion: The picture defined by the laboratory tests was considered to be fairly typical. A diagnosis of thyroid failure was offered and thyroid medication instituted. A subsequent report from the patient's physician was to the effect that shortly after beginning treatment the patient had conceived and borne a normal child.

CASE S-1528. This case is particularly interesting. It is one of the series of sterility studies which the authors and their colleagues have been conducting for some time. The work in general will be described elsewhere in the near future. It is enough to say here that it involves a very thorough study of both partners to the marriage, one phase of which deals with possible endocrine factors.

The patient's chief complaint was the sterility of his marriage, as in the course of three years his wife had failed to conceive. The patient himself was somewhat asthenic and had been so for something over a year. The removal of an abscessed tooth during this period produced only a slight temporary relief from this symptom.

Family History was not significant.

Past History: The patient reported the minor ailments of childhood, scarlet fever, lobar pneumonia, and a questionable attack of small-pox in childhood. He had a mild attack of influenza at the time of the epidemic. There had been a moderate loss of hair. He was

both astigmatic and myopic and showed a susceptibility to rhinitis. He complained of coldness of the extremities and reported some dermographia.

Physical Examination showed a well nourished, slightly obese white male, 34 years of age. The hair was thin, and there was a partial alopecia. The remaining examination gave substantially normal findings.

Laboratory Summary: The patient was slightly above predicted weight, had a normal lung capacity and a basal rate of —26 per cent with low blood pressure, slow pulse, and a slightly sub-normal temperature. The urine was normal except for a high residual fraction in the nitrogen partition. The sugar tolerance was normal; the blood, lymphoid in type. In the sterility study the wife was eliminated as a contributing factor.

Genitourinary Study: No physical abnormalities were found, while the condom specimen was normal in regard to the number, motility, and morphology of the spermatozoa. A post-coital examination showed the presence of spermatozoa, about half of which were dead or non-motile.

Cardiogram: Normal.

Discussion: The laboratory examination demonstrated a clear-cut thyroid failure in the husband. The chief interesting feature lies in the fact that on the basis of the condom specimen the husband would have been eliminated as a factor in the sterility equation under the ordinary conditions of practice. The patient was placed on thyroid medication, the wife conceived inside of two months, and after an uneventful pregnancy was delivered of a normal child.

GROUP V. DEAFNESS.

CASE S-407. The patient's chief complaint was of a progressive deafness which had lowered his aural acuity in the left ear so that only loud noises could be apprehended. In the right ear the hearing was poor but the impairment less pronounced. The condition began at the age of 30 involving first the left ear only. He had been troubled with tinnitus.

Family History: The mother suffered from the same complaint. The remaining family history was irrelevant, except for one aunt who was insane.

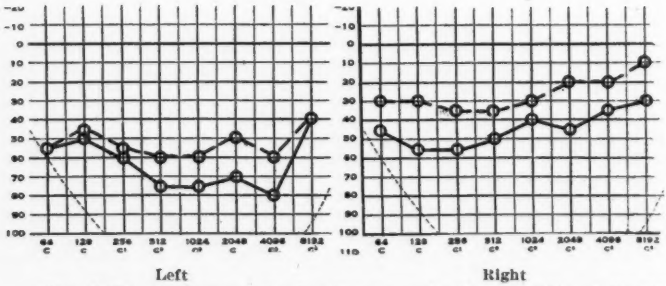
Past History: The patient had the usual childhood ailments but had been perfectly well during his adult years.

Physical Examination: The patient was a well-developed male of 40 with an obesity of general distribution; the muscles were flabby, and the mental reaction sluggish. Both ears exhibited deafness which in the left was more pronounced. The remaining findings were normal.

Laboratory Summary: The patient was overweight. His basal rate of —22 per cent derived from a not altogether satisfactory test. The true rate was probably somewhat lower. There was a high residual nitrogen in the urine and a slight relative lymphocytosis.

Audiogram (see Plate) showed marked loss of hearing in both ears, more pronounced in the left.

PLATE III



Case S-407. Audiograms showing improvement after 6 months of thyroid medication.

Discussion: It was not possible to make as thorough a study on this case as was desired, but a tentative diagnosis of thyroid failure was offered as being the most probable condition. The patient responded well to thyroid medication, and six months later there had been a definite improvement in hearing, as shown by the second audiogram curves (see Plate).

CASE S-1466. The patient's chief complaint was of deafness in the right ear which had begun about a year before without any apparent cause. It had been progressive, although at the time of the examination it was felt to be at a standstill. She experienced tinnitus and exhibited paracusis.

Family History: There was a marked history of cancer on the paternal side.

Past History: The patient recorded minor ailments, an attack of influenza during the epidemic, followed by arthritis, for which she was under treatment. Four years previously she had been operated on for a felon and in the preceding October an appendectomy had been performed. She complained of dyspnoea, some palpitation, and intermittent constipation. Her menstrual history was not remarkable. For some time the patient had been very fatigable. She had gained slightly in weight. With somewhat unusual self-perspective she stated that she had become very irritable.

Physical Examination: The patient was a well-developed, well-nourished girl of 19. During the examination there was a constant slight movement of hands and feet, occasionally of the body and extremities. The eyes were normal; there was no tremor of the tongue; the thyroid was slightly enlarged. She exhibited some tenderness near the appendectomy scar. There was no tremor of the hands but the fingernails were bitten off. The skin was dry and on the legs showed fine scaling.

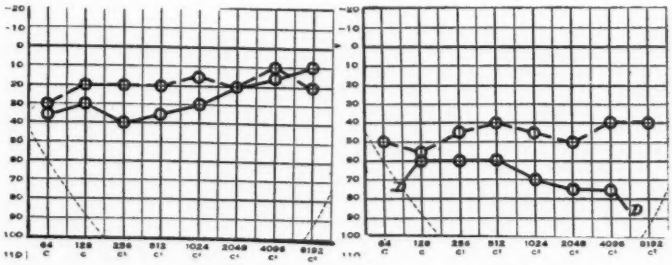
Laboratory Summary: The patient's weight agreed with prediction. The basal rate was —12 per cent, under fairly satisfactory conditions (v. s.). The blood pressure was somewhat low, the urine small in volume, concentrated and containing an abnormally high residual nitrogen fraction. The sugar tolerance was slightly depressed. Blood chemistry and morphology were normal.

Neurological Examination: No evidence of organic nervous disorder was found.

Pelvic Examination gave normal findings.
Cardiogram: Normal.

Audiogram (see Plate) showed marked loss of hearing in the right ear and some loss in the left.

PLATE IV



Left Right

Case S-1466. Audiograms showing improvement after 8 months of thyroid medication.

Discussion: The patient seemingly presented a thyroid dysfunction, not impossibly of the transition type. The basal rate of —12 per cent was felt to be certainly above the truth, and the cautious exhibition of thyroid medication was recommended. Eight months later the patient returned for a test of the aural acuity, and the audiogram (see Plate) showed some improvement in the left ear and marked betterment in the right.

TABLE XIX

		Familial Influence			
Case Number		S-1371	S-1456	S-1520	S-1438
Sex		M	M	F	M
Age	(yrs.)	54	19	18	15
Height	(cm.)	170	182.5	166.5	171.6
Weight	(kgm.)	57.5	60.5	53.2	56.8
Weight Deviation	(%)	+1	−15	−12	−1
Lung Volume Deviation	(%)	−13	−3	−9	+2
Basal Rate Deviation	(%)	(−10)	−31	−30	−21
Blood Pressure	(mm.)	138/86	108/64	102/70	108/66
Pulse Rate	(per min.)	54	67	60	62
Temperature	(deg. F.)	97.7	97.0	98.4	97.8
Alveolar CO_2	(mm.)	57	48	41	42
Urine Volume	(cc.)	1510	1280	1250	560
Spec. Grav		1.015	1.024	1.015	1.026
Albumin		+	0	+	0
Casts		0	0	0	0
Sugar		0	0	0	+
Total Nitrogen	(gms.)	9.70	11.91	7.38	7.20
Residual Nitrogen	(%)	5.7	11.7	4.7	11.9
P. S. P. (2 hours)	(%)	37	36	59	57
Galactose—Normal	(gms.)	30	30	40	30
Observed	(gms.)	30	not	not	not
Deviation	(%)	±0	done	done	done
Blood—N. P. Nitrogen	(mgm.)	32	30	30	27
Uric Acid	(mgm.)	2.8	3.3	3.8	3.4
Sugar	(mgm.)	87	87	96	87
Haemoglobin	(%)	80	85	75	95
Erythrocytes	(10^6)	4.00	5.59	4.29	4.93
Leucocytes	(10^3)	5.00	5.20	9.05	5.00
Neutrophiles	(%)	52	56	62	56
Lymphocytes	(%)	42	38	35	35
Eosinophiles	(%)	0	0	1	1
Monocytes	(%)	5	5	2	7
Misc	(%)	1	1	0	1

GROUP VI. FAMILIAL INFLUENCE.

While it is a frequent record that there is a constitutional tendency in thyroid disease, the cases given in the table above show this rather strikingly. Each one of them taken alone probably defines a case of thyroid failure. No two of them are exactly alike in the general laboratory picture. The father was the first member of the family to be admitted to the clinic, his presenting difficulty being asthenia of comparatively brief duration. His history showed a susceptibility to infection which dated back to early childhood. He had always been constipated and had developed some minor paraesthesias. The physical findings were substantially normal. His basal rate as recorded was distinctly above the truth. The urea index was distinctly below the normal, and this coupled with his low phthalein output and the urine examination suggested a slight lowering of kidney permeability. Radiographic findings were normal, but a laryngological examination demonstrated infected tonsils. Other features of the examination can be seen in the table.

The oldest son was the tall, thin atypical "thyroid failure." Fatigability was his principal difficulty. He also had frontal headache, chronic catarrh, and an earlier acute sinusitis with some paraesthesias of the extremities. His remaining examination was not striking except for a history of jaundice some years before. The

TABLE XX

		Hyperthyroid			
		1	2	3	4
Case Number		B-953	S-1895	S-1188	S-1596
Diagnosis		+	+	+	+
Sex		F	F	F	F
Age	(yrs.)	6	72	38	23
Height	(cm.)	115.5	161.0	162.0	161.0
Weight	(kgm.)	17.7	48.0	45.0	85.9
Weight Deviation	(%)	−13	−18	−29	+35
Lung Volume Deviation	(%)	−56	−39	−35	−22
Basal Rate Deviation	(%)	+18(?)	+22	+44	+55
Blood Pressure	(mm.)	120/55	170/82	122/50	136/58
Pulse Rate	(per min.)	116	100	92	122
Temperature	(deg. F.)	99.2	98.8	98.0	98.6
Alveolar CO_2	(mm.)	38	41	44	44
Urine Volume	(cc.)	170	960	960	1400
Spec. Grav		1.026	1.014	1.023	1.014
Albumin		+	+	0	+
Casts		0	0	+	0
Sugar		0	+	+	0
Total Nitrogen	(gms.)	2.03	3.74	8.91	6.60
Residual Nitrogen	(%)	7.7	7.2	12.8	8.3
"Urobilinogen"		0	0	0	0
Phen. Suloh. Phthal.	(%)	61	69	55	48
Galac. Tol. Deviation	(%)	−50	−	−	−
Non-Protein Nitrogen	(mgm.)	30	32	29	26
Uric Acid	(mgm.)	3.3	3.0	2.7	2.6
Sugar	(mgm.)	93	105	109	75
Haemoglobin	(%)	95	80	90	88
Erythrocytes	(10^6)	5.14	4.68	4.93	4.32
Leucocytes	(10^3)	6.75	5.05	7.90	9.50
Neutrophiles	(%)	42	70	53	68
Lymphocytes	(%)	35	25	38	29
Eosinophiles	(%)	10	1	1	1
Monocytes	(%)	13	4	8	2
Misc.	(%)	0	0	0	0

1. Young child, exoph. goiter. B. M. slight; sugar, large change.
2. Incipient recurrence long after operation.
3. Prompt recurrence after operation.
4. Recurrent after operation with obesity.

physical findings were substantially normal. X-ray studies showed obstruction of the nasal fossae.

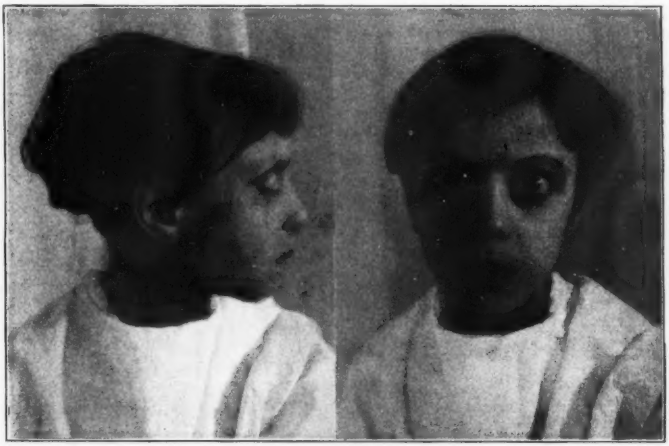
The second child, a daughter, is also an atypical "thyroid failure." The history as given is not suggestive and the physical findings were equally normal.

The youngest member of the family is perhaps less certainly hypothyroid. He did show a slight thyroid enlargement, the only one of the group giving any evidence of goiter. We were unable to study this case as thoroughly as desired and are by no means certain of the diagnosis. The slight glycosuria is a disturbing note, although several causes not incompatible with a thyroid failure could produce it. That he is "endocrine" is obvious. Further study would be necessary to fix with certainty the focus at fault.

GROUP VII. HYPERTHYROID.

The following group of cases have been selected as presenting certain possible interesting points in connection with a definite hyperthyroidism. The enormous general literature dealing with the condition renders it unnecessary to discuss cases falling in any of the conventional groups.

PLATE V



Case B-953

CASE B-953. This little patient, a child of five, was referred to us with all of the outward evidences of well-marked exophthalmic goiter. The presenting complaint was her bulging eyes coupled with a marked nervousness. At about the age of a year and a half the mother noted that the child's eyes were beginning to bulge and that she was becoming nervous. The condition has been progressive, and because of her unusual appearance she has had difficulty with her schoolmates and had to be withdrawn shortly after entrance into her school. She had been under intermittent observation but without treatment.

Family History: The child is the oldest of three children, the other two being normal. The remaining history is not informative.

Past History: She was normally delivered, and breast fed for the first six months. She had measles at the age of four. The vision was not very good. She was subject to head colds and to sore-throats. She experienced no difficulty in breathing; the bowels were regular; there has been excessive perspiration on hands and feet and a skin eruption on the former.

Physical Examination: The patient was a well-developed but thin Italian child, 5 years of age, presenting a very marked exophthalmos, and moderate symmetrical thyroid enlargement. There were pulsations all along the anterior and lateral surfaces of the neck, and a well-developed bruit. The child showed lid lag and a positive Stellwag sign. The tonsils were large, cryptic and apparently infected. There was tachycardia and apparently some cardiac enlargement. The pulse pressure was very high. There was a slight fine tremor of the fingers, the knee jerks were equal and very active. The extensor test of the thigh suggested by Dr. Lahey was positive.

Laboratory Summary: The child was somewhat underweight and much below her predicted lung volume. A series of basal rate determinations gave a moderate increase above prediction. The standards for children of this age are not well defined and the value given represents a probable value from a series of different comparisons. There was tachycardia, a slightly febrile temperature, and a large pulse pressure, to which attention is again called. The urine was very scanty and contained albumin. The residual nitrogen fraction was normal. The sugar tolerance was half the normal level. The blood morphology showed a 10 per cent eosinophilia.

Radiography: There was no substernal enlargement; the heart was normal; the lungs showed mottling at both bases; the skull was normal; the optic canals were symmetrical and 4 mm. in diameter.

Skin Examination: This defined the eruption on the hands as punctate purpuric lesions of unknown etiology. In the examiner's opinion they were not associated with the exophthalmos.

Surgical Examination: "The thyroid was moderately enlarged. The exophthalmos was disproportionate to the apparent degree of toxemia."

Chest Examination: There was no evidence of present pulmonary disease. The cardiac enlargement was confirmed.

Neurological Examination: The findings were normal except for those characteristic of exophthalmic goiter.

Nose and Throat Examination: Cryptic tonsils of moderate size were found.

Cardiogram: This showed a normal mechanism with accelerated (125-135) rate. There was some evidence of possible auricular hypertrophy.

Eye Examination: The discs were yellowish and there was a thin retinal pigment with the choroidal vessels visible. The sclerae were bluish. The fields could not be obtained owing to the age of the patient.

Discussion: That the patient presented goiter with exophthalmos was obvious. Apparently, however, the toxicity of the gland was low insofar as the basal rate would be taken as an index. On the other hand the sugar tolerance was much depressed, and while some depression would be anticipated with an overactive thyroid, the relative

degrees were disproportionate if the usual case be taken as a criterion. Suggestion of a congenital internal hydrocephalus was made by one of our associates, but x-ray examination of the skull gave no supporting evidence. As the child was not toxic to any marked degree she was discharged from the hospital without treatment with recommendation that she return within a few months for further study. In our experience primarily overactive thyroids at times undergo a spontaneous functional involution. Further, the extreme youth of the little patient seemed to warrant delay, since no evidence of marked toxicity was apparent. Two months later, however, the child having presented certain disturbing symptoms, she was referred to the Lahey Clinic for operation. We are much indebted to Dr. Robert L. Mason for the following information:

"She was brought to the Deaconess Hospital on May 17. With her history you are, of course, familiar. On examination she presented a rather marked exophthalmos. The thyroid was uniformly enlarged and had the firm, elastic consistency of a hyperplastic gland. Her pulse rate was 132; weight was 40¾ pounds. The remainder of her general physical examination was essentially negative. Basal metabolism test the following morning showed a rate of +60. We believed the child to present a definite case of primary hyperthyroidism. She was placed on a pre-operative regime which included five minims of Lugol's solution three times a day, a high calorie diet, and rest in bed. On May 31st, her metabolism had dropped to +4; her pulse rate to 80, and she had gained 1¼ pounds. We thought her ready for operation.

"On June 1st, operation was done. Four-fifths of a definite hyperplastic gland was resected. Pathological examination of the excised thyroid tissue showed it to be primary hyperplasia with moderate involution. There was a mild reaction following operation, which, however, had entirely subsided by seventy-two hours. Her subsequent course was satisfactory and uneventful. On discharge, she was doing very well. She was given a prescription of five drops of Lugol's solution taken each week for three months, at the end of which time she was to have a check-up for metabolism."

In the case of this child we are by no means certain that the obvious thyroid condition was not complicated by some other and extraneous effect. The preliminary study gave several possible evidences that this might be the case. She will be studied later in the hope that additional light can be thrown on the condition. It is quoted here, partly because of the somewhat unusual youth of the little patient and because it possibly illustrates the sugar anomaly of which note was made in the earlier section. In this connection we have had opportunity to make a more complete study of an adult woman in whom no complicating superimposed effect could be demonstrated. The significant data are given in the following table:

TABLE XXa

Date	Interval (Week)	Blood Pressure	Pulse	Basal Rate	Weight	Sugar Tolerance	
Dec. 6, 1926	0	132/54	84	+6	52.2		
Dec. 13, 1926	1	118/50	86	+11	52.1		
Dec. 27, 1926	2	.....	....	....	....	−75%	
Jan. 7, 1927	2	128/48	100	+16	49.6		
Jan. 15, 1927	1	———	Operated	———	———		
Jan. 22, 1927	1	126/42	78	+12	47.7		
Mar. 14, 1927	7	108/52	71	−15	51.4		
Mar. 28, 1927	2	.....	....	....	....	+50%	
April 25, 1927	4	116/58	73	−11	52.2		
June 6, 1927 to Dec. 1, 1927	6	112/58	80	+2	50.2		10 tests
	24	110/60	88	+6	51.6		
Dec. 28, 1927	4	.....	....	....	....	−50%	
Feb. 3, 1928 to May 4, 1928	9	120/48	102	+17	49.0		5 tests
	13	138/68	88	+31	49.3		
May 18, 1928	2	130/72	96	+35	48.8		
May 24, 1928	1	———	Operated	———	———		
July 7, 1928	2	116/68	52	−28	54.5		
July 14, 1928	1	118/70	64	−31	55.0		
July 16, 1928	..	.....	....	....	....	±0	

This patient was a young woman of 29, first seen on December 6, 1926. She presented a clear-cut outward appearance of exophthalmic goiter, was emaciated, intensely nervous, and showed all the conventional stigmata. She gave a history of good health except for a poor appetite up to the preceding July. At this time her appetite became voracious, and at the same time her friends called attention to the protrusion of the eyes. The condition progressed and in September her attention was called to the palpable thyroid enlargement. The family history that she gave was entirely irrelevant. In her own personal history, an attack of measles at the age of 4, and three or four minor infections during the preceding year, were the only points of comment. The menstrual history had been an entirely uneventful one up to a year previously. At this time the periods fell to two days and with a very scanty flow. The basal rate determination showed the normal value of +6 per cent, a pulse rate of 84, and a normal systolic and low diastolic blood pressure. As her basal rate was wholly incommensurate with her patent goiter condition, and the degree of toxicity which she exhibited, it was repeated and +11 per cent recorded. Her sugar tolerance was found to be notably low, at a level, in fact, which we had never before recorded in uncomplicated thyroid hyperactivity. Subsequently the patient became very toxic. A test on January 7 showed a basal rate of +16 per cent, progressive tachycardia and loss of weight. She was operated upon one week later, after the usual period of rest, and shortly dropped to a mild hypofunctional level. There was distinct clinical improvement and during the latter part of this period a sugar test was performed which showed a tolerance 50 per cent above prediction. For the next few months she kept in touch with the Clinic and at the end of about a year from her first contact began to give signs of a renewed toxicity, although the basal rate presented the normal value of +6 per cent. Her sugar tolerance at this time was —50 per cent. Operation was postponed, but in May of the current year it became patent that the condition was progressive with steadily increasing toxicity. A second operation was performed, and the tests since made showed a drop of the basal rate to a frank hypofunctional level, while the sugar tolerance has become normal, the patient has gained weight rapidly, the exophthalmos is greatly diminished, and the patient regards herself as entirely cured. The interesting feature in this case is the marked divergence of the sugar tolerance with the slight variations in the basal rate. This reverses completely the usual thyroid finding in which even marked over- or under-activity of the gland are accompanied by relatively slight changes in the sugar tolerance, and in approximately two-thirds of our cases by no departure from the normal. A possible explanation already touched upon could lie in the existence of a second hormone produced by the thyroid which under ordinary conditions is but slightly influenced by changes in glandular activity. In a few cases, however, this hormonic influence seems to be the one involved, that agent which controls the oxygen consumption being but slightly influenced. That the patient was toxic there can be no possible doubt. The recession of the symptoms with each of her operations, but more marked with the second, and the absence of any other disorder discernable after careful and thorough study, would seem to indicate a definite thyroid aberration as the cause of her difficulties. The suggestion offered above is no more than a suggestion. We have had, however, a few cases in the past (4 or 5) which have shown analogous abberrations of carbohydrate metabolism. In cases in which thyroid disease was definitely established and no superimposed effect could be demonstrated, the fact that, from the clinical side, individual patients will show their greatest response to thyroid

extract alone, to thyroxin alone, or to a judicious blending of the two, may well be pertinent to this thesis.

CASE S-1895. This case was reported as of possible interest as demonstrating a recurrent hypothyroid condition, after a considerable interval, in a woman of advanced years. The patient presented as her chief complaints bronchial asthma which had begun after her thyroid operation; arthritis in the back and left leg, from which she had suffered for the past four years; a general itching of the body similar to that experienced previous to the operation, and which was of but brief duration; tachycardia which had developed in the past few weeks.

Family History: The father died of diabetes, the mother of cancer. Many of the immediate family were above average height. No other case of thyroid disease was recorded.

Past History: The patient reported the minor childhood diseases, but none of the graver complaints of adult years. A thyroidectomy in 1921 was her sole operation. She had recently developed what she termed a "thyroid headache" similar to that experienced previous to her operation. There had been marked loss of hair at that earlier time, and again recently. The teeth had all been removed, and there was more or less soreness in the mouth, which latter was of recent date. She complained of dyspnoea and palpitation at the two intervals significant in relation to her thyroid. She had lost 15 lbs. in the past four months. Her menstrual history was uneventful. She was very fatigable. During her long married life she had one miscarriage and had borne one child, which subsequently died of epilepsy.

Physical Examination showed a fairly well-preserved but undernourished woman of 72 whose hair was coarse and thin, no exophthalmos, teeth all gone and the buccal mucous membrane normal. There was no evidence of thyroid enlargement, there were minor abnormal sounds in the chest. Arteriosclerosis was present. There was some tachycardia and a few minor neurological findings which were not confirmed by the neurologist.

Laboratory Summary: The patient was 18 per cent underweight and significantly below her predicted lung volume. There was a hypertensive blood pressure, rapid pulse, urine showing both albumin and casts, and protein intake far below a maintenance level. The remaining findings were not strikingly significant.

Radiography of the chest showed scattered calcified nodes along the track of the large bronchi and emphysema. Both antra were obscured.

Neurological Examination noted the tremor of the hands, but gave no evidence of organic neurological lesion.

Cardiogram showed simple tachycardia with premature ventricular beats.

Chest Examination confirmed the harsh respiratory sounds over both bronchi, together with some peribronchial dullness.

Laryngological Examination gave entirely normal findings.

Discussion: The picture here is typical of a mild and, in this case, recurrent hyperthyroidism. Whether the infected antra played any part in this event must be a matter of speculation. X-ray

therapy was recommended, and we understand that the patient has shown definite improvement.

CASE S-1188. The following case is typical of the recurrence of toxicity shortly after a successful operation for an initial hyperactivity. The patient's chief complaint was of nervousness and palpitaton. The former condition she dated from the birth of her only child five years before. The palpitation was noted somewhat later, but constituted an integral part of the picture. From the patient's history it was patent that the nervousness dated back to childhood and that the present complaint derived from exacerbation produced, in part, by her added domestic responsibility and, in part, from other coincident social problems.

Family History: The mother died of cancer. The remaining history was irrelevant.

Past History: Beyond measles and a tonsil and adenoid operation nine years previously, the patient's history was singularly uneventful. She had had some constipation, some nocturia, but in the main was free from illness or general complaint. She had been married for seven years, had borne the one child noted above, and had not conceived again. Her menstrual history showed an onset at 14 and a typically irregularity with both increase and diminution in the interval. The periods were fairly normal. She was found to be irritable, unreasonable, and egocentric. "In her hurry to convey an idea she talks so rapidly that the words become all jumbled together and the entire face goes into a nervous quiver."

Physical Examination: The patient was a fairly developed but distinctly emaciated woman of 33. The hands and feet perspired freely. There was no exophthalmos, but the tongue and hands showed fine tremor on extension. The thyroid was not significantly enlarged but venous pulsations were visible in the neck. The heart showed a marked systolic murmur, heard best over the pulmonic area, transmitted toward right and upward; the apex impulse was visible, there was a distinct tachycardia and a characteristic high pulse pressure. The knee jerks were slightly hyperactive.

Laboratory Summary: The patient was 29 per cent below her predicted weight and significantly below her predicted lung capacity. The basal rate was +44 per cent, with a variable and rapid pulse. A few hyaline casts were reported in the urine and there was very slight glycosuria. The urinary residual nitrogen was high. The blood was lymphoid in type.

Discussion: The patient presented a fairly typical thyrotoxicosis, and in November of 1927 a portion of the gland was removed. The basal rate, which had ranged from 40 per cent upward, promptly dropped to —10 per cent on November 11, and —12 per cent on December 8. The pulse had dropped to the low fifties; the blood pressure, while low, showed a more nearly normal pulse pressure. In April, however, of the current year there was a return of the patient's symptoms, there having been previously practically complete relief. On May 31, the basal rate was +26 per cent, with a pulse rate of 66. She had begun to lose weight rapidly. She was admitted to the hospital and with complete rest her basal rate dropped to +16 per cent. For outside reasons she decided to postpone operation for a brief time,

but it is patent that there has been a recurrence of the toxicity and that a second operation in the near future is inevitable. The rapid recurrence in the case after a period of several months of seemingly complete amelioration is the noteworthy feature.

CASE S-1596. This case is cited for the reason that it presents recurrent toxicity after an earlier operation, coexisting with marked obesity. The patient's chief complaint was nervousness and tachycardia. She was also much overweight and the legs were noticeably large, which constituted a serious embarrassment to her. During the day they seemed to get larger, but were at all times disproportionately large. She dated her nervousness back about one year and had noted since its onset that there was a recurrent tightness in the throat on swallowing.

Family History: The father had died of thyroid failure and there was a history of cancer in the earlier generations.

Past History: Barring scarlet fever and measles in childhood and a susceptibility to tonsillitis, the medical history was substantially irrelevant. The catamenia began at nine, showed some irregularity with increased interval, and a gradual diminution in the length and amount of the periods. The obesity goes back to early childhood and has not been controllable by diet.

Physical Examination: The patient was a well-developed, generally obese young woman of 23. There was no exophthalmos, a very slight thyroid enlargement, marked tachycardia (140); the legs were very obese, but there was no pitting edema of either legs or ankles; the hands showed a definite tremor on extension.

Laboratory Summary: The patient's weight was 35 per cent above prediction; she showed a basal rate of 55 per cent above the normal, with a pulse rate of 122. The urine volume was normal; albumin was recorded, but the residual nitrogen fraction was normal. The blood sugar was sub-normal; the blood showed a slightly low value for the erythrocytes.

Cardiogram showed a normal function and rapid rate.

Diagnosis: A diagnosis of "toxic thyroid" was offered and the patient was operated upon with a very definite improvement in both clinical and laboratory signs. As the basal rate fell the body weight showed an upward tendency. In the past few months, however, there has been a slight loss of weight, and in May of the current year the patient showed a body weight of 85.7 kgm., a basal rate of +54 per cent, and a pulse rate of 112; in other words, practically the identical picture which she had at first presented. Operation was recommended and we are advised that a further partial thyroidectomy has been successfully performed with marked improvement in the patient.

The last two cases illustrate a fairly rapid recurrence in two definitely opposite types. In the first case (S-1188), the patient gave a history of previous glandular medication which had only served to intensify her symptoms. The second patient with her enlarged thyroid and her very definite obesity might well have been classified as a dysfunctional type, and also given thyroid medication. Fortunately, however, this did not happen. Another point of interest in the second case was the low level of the protein metabolism, taken in conjunction with the definitely hyperactive state of the thyroid.

TABLE XXI

	Pseudo-Nephritis		1	2	3	4
Case Number	B-110	B-110-a	B-560	S-1396	B-738	B-730
Diagnosis	—	—	—	—	— (surg.)	—
Sex	F	F	M	F	F	M
Age (yrs.)	53	53	11	24	52	26
Height (cm.)	157	157	134.0	152.0	176.3	190.5
Weight (kgm.)	69.5	59.0	29.1	69.0	85.0	81.9
Weight Deviation (%)	+26	+7	−10	+30	+7	*(+7)
Lung Volume Deviation (%)	−48	−44	−16	−12	−35	−26
Basal Rate Deviation (%)	−32	+35	−52	−39	(−16)	−40
Blood Pressure (mm.)	124/80	116/68	102/60	90/74	150/84	120/68
Pulse (per min.)	72	78	76	51	64	60
Temperature (deg. F.)	98.2	98.2	97.0	97.2	97.8	97.4
Alveolar CO_2 (mm.)	37	(33)	41	36	45	50
Urine Volume (cc.)	750	580	1700	1310	1230	620
Spec. Grav.	1.016	1.018	1.010	1.012	1.019	1.031
Albumin	0	0	+	0	+	0
Casts	0	0	++	0	0	0
Sugar	0	0	0	0	0	0
Total Nitrogen (gms.)	4.22	5.90	7.85	5.17	10.33	8.33
Residual Nitrogen (%)	6.5	5.0	12.9	9.5	8.5	12.4
"Urobilinogen"	0	0	0	0	0	+
Phen. Sulph. Phthal. (%)	32	55	21	32	39	48
Galac. Tol. Deviation (%)	±0	±0	+33	not done	±0	±0
Non-Protein Nitrogen (mgm.)	36	26	33	32	35	31
Uric Acid (mgm.)	4.9	3.2	2.5	3.2	3.8	3.3
Sugar (mgm.)	87	77	87	85	93	100
Haemoglobin (%)	90	95	100	85	85	90
Erythrocytes (10^6)	4.83	4.72	5.50	4.20	3.78	4.76
Leucocytes (10^3)	5.25	6.05	11.70	7.30	3.50	5.70
Neutrophiles (%)	48	51	26	49	47	56
Lymphocytes (%)	49	40	71	40	44	32
Eosinophiles (%)	0	1	0	2	3	2
Monocytes (%)	3	8	3	9	6	9
(Basophiles) (%)	0	0	0	0	0	1

*See discussion of case.
1. Presenting so-called "Epstein's Nephrosis."
2. Characteristics cardiac findings.
3. Complicated with primary anaemia.
4. Complicated with earlier hyperpituitarism spontaneously arrested.
* Sitting Height Index < 0.50.

GROUP VIII. "PSEUDO NEPHRITIS"

CASES B-110 AND 110-a. The patient's chief complaint as presented was a bloating of the face, which gradually extended over the chest and arms. This at first began some two months before admission, but probably had been going on for some time prior to this. She had been getting progressively fatigable and nervous, felt that her aural acuity was diminishing, and that there was a general failure of all of her powers.

Family History was not informative.

Past History: The patient reported all of the minor ailments of childhood and pneumonia at 36 complicated by a secondary anæmia. The deafness really began some 16 years previously, but it had been disquieting only for the last few months. She had been gaining weight recently and suffered from dyspnoea. She had always been constipated; the appetite had been poor. The marital history showed two children and two miscarriages. The catamenial history was normal, including a slow and uneventful menopause, which apparently was completed a few months before her admission.

Physical Examination: The patient was a well nourished, somewhat obese woman of 53, She presented some loss of hearing. The

skin was dry, glossy, and hypertrophic; the eyelids swollen, palpebral fissures narrow; practically all teeth had been removed, those remaining being abscessed; the thyroid was not enlarged: the heart action was slightly irregular, and there was a slight systolic murmur. The remaining findings were substantially normal.

Laboratory Summary: The patient was 26 per cent overweight and had lost nearly half of her predicted lung volume. The basal rate was —32 per cent. The urine volume was scanty, elimination poor. The phthalein output was distinctly below the normal. Protein intake, as shown by the urinary nitrogen, was far below a maintenance level. The blood analysis gave evidence of lowered kidney permeability. The blood showed a marked relative lymphocytosis.

Neurological Examination showed certain paræsthesias, an 8th nerve disturbance, and a possible loss of deep sensation in the right leg.

Eye Examination showed a definite contraction of form and color fields, most pronounced in the upper quadrant, the latter due to lid droop.

X-ray Examination: The sella was normal; the heart showed right-sided enlargement.

Pelvic Examination: Findings were normal except for minor residua of child-bearing.

Discussion: The possible suggestion of primary anæmia had been ruled out by observations made elsewhere. The picture here presented was consistent with a hypothyroidism with myxedema. The patient was placed on thyroid extract, and two months later returned for a brief series of check observations. Clinically she was greatly improved. The skin had cleared entirely: she had lost 10.5 kgm. weight: the lung volume was slightly better: the phthalein output had risen to a normal level; her nitrogen elimination had improved: while the blood nitrogen values had diminished to levels consistent with her protein intake. While the blood was still lymphoid in type, the degree had diminished, and the general formula far more nearly approached the normal.

GROUP IX. THYROID FAILURE WITH MISCELLANEOUS COMPLICATIONS

CASE B-560. The patient was a boy of 11 whose case had been diagnosed as one of Epstein's nephrosis. Two series of studies were available which had been made at earlier periods. The boy was first admitted to the hospital in January, 1919, then being 4 years of age. He was kept under observation for nearly a year, and was discharged as having chronic parenchymatous nephritis. During this period he had shown marked ascites of the abdomen and, on a number of occasions, quanties of fluid of the order of a quart had been removed by tapping. The urine had shown a characteristic picture. He remained in good health until July, 1921, when he was readmitted in a markedly edematous condition. There had been vomiting for twenty-four hours. The condition progressed, and early in August a decapsulation operation was performed on the right kidney, and in September on the left. There was rapid improvement and he was discharged in November. Three years after a tonsil and adenoid operation was performed, and in March, 1925, he was again readmitted with marked edema. The condition cleared up in a few days, however, and he was discharged with a confirmation of the earlier diagnosis. He was admitted to this

service in June, 1926, with marked anasarca and ascites. Again the condition gradually cleared up and in July, 1926, further study was undertaken.

Family History: A general history of renal disease was obtained.

Past History: Beyond the facts already discussed, the patient reported scarlet fever, influenza, several minor ailments, tonsilitis, and bronchitis.

Physical Examination showed a somewhat undersized boy of 11, with face somewhat full and puffy, general nutrition fair; the nose was broad and flattened, the nares not obstructed. He showed a minor cervical adenopathy, but no thyroid enlargement. The heart showed a soft systolic murmur at the apex, which was not transmitted. The lungs and abdomen substantially normal. The remaining findings were not significant.

Laboratory Summary: At the time of this examination the acute phase had passed. The urine volumes were ample, albumin and casts were both present; elimination was good; the residual nitrogen was high; the phthalein output at this time distinctly low. The boy was 10 per cent underweight and had shown a basal rate of —52 per cent. This very low level would be influenced, naturally, by any residual trapping of fluid, but as the lad was 10 per cent underweight and gave no positive evidence of the presence of fluid, the value observed was felt to be approximately correct. The blood pressure was low, the temperature slightly sub-normal. The sugar tolerance at this time was slightly above the normal. The blood constituents were normal and gave no evidence of retention. There was a slight leucocytosis, with very marked increase in the lymphocytic fraction.

X-ray Examination: The skull, sinuses, and kidneys were normal. The sella was normal, except for some evidence of bridging between the clinoids.

Eye Examination: Fine granular pigmentations throughout the retinæ ("pseudo-snuff fundi"), which is probably normal. There was a slight blind spot enlargement and a possible slight contraction of the color fields, which could not be confirmed, however, a few days later.

Studies of the urine showed no loss of concentrating power in the kidney, there being a variation of ten points. The general picture was one of renal irritation without functional damage.

Cholesterol and fibrinogen of the blood were high; plasma protein, low.

Discussion: With just recognition of the kidney condition, the remaining picture was essentially that of a thyroid failure. Part of the earlier work on this patient had been done elsewhere, and we have reason to believe that some thyroid extract had been exhibited, but no chronological record was available. On May 28, a basal determination was carried out which showed a low blood pressure, a rapid pulse, and a rate recorded as —15 per cent. As the patient was nervous, however, this could be discounted materially. On June 10, with subsiding pulse rate, the basal rate was about —50 per cent. On June 23, the pulse was above 100 and the basal rate +18 per cent. Three days later the pulse was 88 and the basal rate +11 per cent. On July 6, the pulse was 72, temperature and blood pressure definitely low, and a basal rate of —26 per cent was obtained. As will be seen in the table, the basal rate again went still lower, and then, on thyroid medication, there was a prompt return to the normal level. The

patient was discharged shortly after in a greatly improved condition. We have not been able to effect a later contact, but from the fact that there have been no further hospital entries recorded it seems fair to assume that there have been no serious recurrences.

In Epstein's original papers, he lays great stress on the blood cholesterol and fibrinogen. So far as we are informed, no adequate studies have been made on the influence of thyroid failure on these substances. While this is not the place to carry out a discussion, the writers are entirely unconvinced as to the existence of the so-called Epstein nephrosis as a disease entity. Certainly in the present case there is a typical picture of thyroid failure, which is supported by the patient's very prompt response to thyroid medication. This case opens up a number of lines of study, some of which are at the present being prosecuted. Whether there be a definite relationship between kidney and thyroid function, or whether the former be influenced by the metabolic disturbance incident to hypofunction of the latter, is a question that awaits future resolution. The case is offered here only as it presents certain points of general interest.

CASE S-1396. This patient is included in the group not because she presented a complication of thyroid disease, but because of a very interesting series of cardiograms produced by her condition and subsequent medication.

The chief complaint was of nervousness and fatigability. Four years prior to admission her husband had died after one year of married life. This produced a profound emotional shock, followed by loss of weight and general nervous imbalance. One year subsequently she began to increase in weight, and this had progressed to a point of definite obesity. During the past year she had had numbness and pricking sensations in the hands and had become relatively insensitive to hot objects.

Family History: Not significant.

Past History: Beyond minor ailments of childhood, the patient's life had been medically uneventful. She did not become pregnant during her brief marital experience. She complained of some dyspnoea, constipation, and some indigestion with flatulency. She had become decidedly asocial since the onset of the present illness. The menstrual history showed a normal onset, but with marked irregularity, the periods occurring from two to three months. The periods themselves were somewhat profuse.

Physical Examination: The patient was a well-developed, obese young woman of 24, presenting the typical facies of myxedema. The hair on the vertex was dark and very scanty, the skin very tough, thick, dry and scaly; palpebral fissures greatly narrowed, eyelids puffy. There was pain on pressure over the right maxillary sinus. The blood pressure was low and there was a marked bradycardia (44). A few scattered rales were reported in the right chest. There was some tenderness in both lower quadrants. The remaining findings were not signficant.

Laboratory Summary: The patient was much overweight. The basal rate was —39 per cent, with very low blood pressure, bradycardia and subnormal temperature. The urine was substantially normal except for poor elimination and high residual nitrogen. Her protein intake was inadequate. The blood showed a definite lymphocytosis.

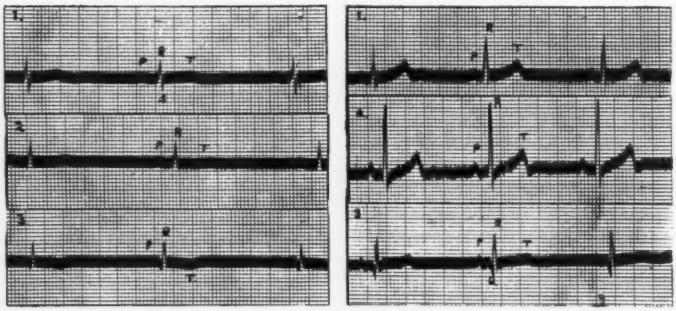
X-ray Examination: Chest, heart and lungs were normal. The teeth showed one unerupted molar and one periapical abscess. The skull was normal.

Pelvic Examination: The findings were normal. The tenderness in the lower quadrants was not confirmed.

Cardiogram: The graph apparently showed a normal mechanism at a retarded rate (see plate).

PLATE VI

Case S-1396. Cardiograms before and after treatment.



March 1, 1927 April 27, 1927

Audiogram: Normal conditions were found.

Laryngological Examination: Tonsils were suspected, but infection could not be demonstrated.

Neurological Examination: Conditions were normal except for findings associated with the myxedema.

Eye Examination: The form and color fields very markedly contracted symmetrically; the blind spots, much enlarged.

TABLE XXI-a

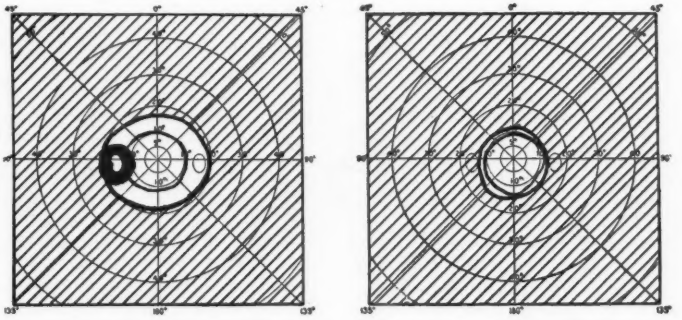
CONTINUOUS RECORD OF CASE OF HYPOTHYROIDISM

Date	Basal Metabolism	Blood Pressure	Pulse	Weight
March 1	—39%	90/74	51	69.0
15	Began medication			
April 2	—11%	102/66	50	62.3
9	—10%	96/50	48	60.5
	Lowered dose			
18	—19%	90/38	46	58.5
	Increased dose			
23	—11%	86/38	44	58.4
30	—10%	94/42	52	57.3
May 16	— 4%	98/54	54	57.5
21	— 3%	98/54	58	57.5

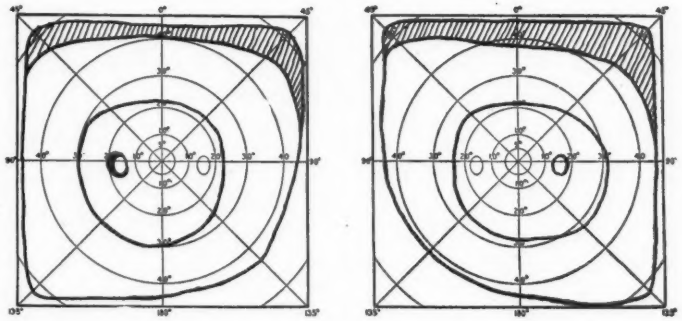
Discussion: The patient presented a typical picture of hypothyroidism with myxedema. She was placed on thyroid medication and in a few weeks obtained a normal basal rate, with the loss of slightly more than 10 kgm (see table). Clinically, she showed the remarkable improvement which may be confidently anticipated in simple cases of thyroid failure. The cardiogram became entirely normal (see plate). An interesting feature was the persistence of the low blood pressure and bradycardia after all of the other findings had become normal. A second eye examination was made and the earlier much contracted fields found to have been entirely corrected except for a slight upper field cutting, due to lid droop (see plate).

PLATE VII

Case S-1396. Eye plots before and after treatment.



March 5, 1927



September 28, 1927

CASE B-738. The patient's chief complaint was of asthenia, which first became remarkable 2 years ago. It had been progressive, and during the preceding four months had become seriously crippling. A diagnosis of thyroid failure had been made, but no thyroid medica-

tion had been given. About four months ago she began to experience numbness and stinging in the extremities, and this had spread somewhat to involve the entire limb. For five years past she has had more or less trouble with eczema. Recently the blood calcium was found to be deficient and iron injections were given.

Family History was not significant.

Past History: The patient had minor ailments in childhood, and in 1907 a partial thyroidectomy. In 1918 the uterus was removed and an appendectomy was done. For the last 2 years there had been almost constant headache. The hair had grown gray and become very dry during the same interval. The eyes were easily fatigable. During the last year she had developed a rash in the mouth, and at times small ulcers with white centers had appeared on the tongue. There was occasional dyspnoea, a tendency to constipation and flatulency. The patient was unmarried; the menstrual history was substantially negative except for scanty periods and termination with the fibroid operation above referred to. Recently she had experienced coldness of the extremities and some edema.

Physical Examination: The patient was a well-developed and well-nourished woman of 52, somewhat above the average height. She exhibited a moderate exophthalmos and a vesicular eruption on the tongue. The skin was dry and hypertrophic throughout, with eczematous patches on the extremities; brown macular eruptions were observed on both legs. There was a slight, coarse tremor of the hands and the reflexes were sluggish.

Laboratory Summary: The patient was 7 per cent overweight. The basal rate as recorded was —16 per cent, but this was probably somewhat above the truth. The blood pressure was slightly high. The urine showed albumin, and the residual nitrogen an upward tendency. The sugar tolerance was normal. The blood analysis gave no evidence of retention. The blood morphology showed an anæmia of the primary type with a leukopenia.

Skin Examination defined a papulo-vesicular eczema and suggested that the pigment areas were due to Schamberg's disease.

Neurological Examination demonstrated loss of bone conduction in the lower extremities and noted the paræsthesias already recorded.

X-ray findings of the skull and sella were normal.

Eye Examination: The fundi showed a slight amount of vascular sclerosis; there was cutting of the upper form fields, due to lid droop.

Neutral Red Test: Dye was not recovered in two hours.

Gastric Analysis: No free hydrochloric acid was found.

Diagnosis: The patient presented a post-operative hypothyroidism complicated by a primary anæmia. The latter was shown to be in a state of remission, with characteristic regeneration, as evidenced by repeated typical blood examinations.

CASE B-730. This case presents several points of interest, as a current endocrinopathy is complicated by residua of an earlier and different endocrine disease.

The patient's chief complaint as given was of pain in the back, from which he had suffered for three or four weeks, and which followed a period of hard manual labor. As a matter of fact, the patient was sent in for the evaluation of certain physical abnormalities, coupled with a definite mental arrest.

Family History: Irrelevant.

Past History: The patient reported minor ailments, smallpox at 21 (there having been an unsuccessful vaccination at the age of 18), several traumatic injuries not germane to the present study. He had had severe frontal headaches for the past year. All of his teeth were removed at the age of 22 because of severe caries. Prior to this, there was almost daily toothache. Up to the age of 16 he was of normal size. He then began to grow rapidly and in a relatively short time reached his present height of 190.5 cm., which is probably greater, as the patient's posture is poor and he exhibits a definite stoop. He complained of an occasional fleeting pain lasting only a minute or two in the upper right quadrant.

Physical Examination: The patient was a noticeably tall, somewhat spare young man, 26 years of age. There was some enlargement of the frontal bossæ and a definite protrusion of the lower jaw. The teeth, as noted above, were all missing. The tonsils were enlarged, and there was a slight thyroid enlargement. In addition, a slight inguinal and cervical adenopathy was noted. The testicles were somewhat atrophic, the skin dry, the posture, as noted above, was poor. Mentally, the patient was slow and immature and definitely below an average intelligence. He further presented a speech difficulty, articulation being thick and obscure.

Laboratory Summary: By the Dreyer standard, the patient was 7 per cent overweight, but as the sitting height index is slightly less than 0.50. he was actually slightly underweight. There was some loss of predicted lung volume. The basal rate was —40 per cent, with a tendency to lowered blood pressure and bradycardia less clearly shown in the present than in other records. The temperature was slightly subnormal. There was oliguria, a high residual nitrogen, and a somewhat low phthalein output. The sugar tolerance was normal; blood constituents normal; a blood morphology, substantially normal.

Cardiogram: This shows a normal mechanism with simple bradycardia (pulse rate 51).

X-ray Examination: The skull, sinuses, and sella were normal.

Audiogram: Slight general loss of hearing in both ears was noted.

Eye Examination: The discs were yellow, the blind spots greatly enlarged, and both form and color fields notably contracted symmetrically.

Duodenal Function (McClure): The values were all low, indicating a definitely disturbed liver function.

Icteric Index was high.

Van den Bergh: A strongly positive reaction was obtained.

Discussion: This is a case in which the findings are susceptible of several possible interpretations. Its resolution must rest on the basis of probability. The patient's outward habitus is, of course, suggestive of a pituitary overactivity. That such a condition obtained, we believe there can be no question, and, equally, that there was a spontaneous arrest some years before we saw the patient, which left the gland at a present normal level. While it is true that the pituitary could be in a functional transition from an initial hyper- to a terminal hypo-active state. there is nothing in the present study to support such a theory. The level of the basal rate, the bradycardia, the

oliguria, coupled with the absence of a high blood uric acid and an eosinophilia, are all observations against a pituitary diagnosis. True, there is a positive urobilinogen test, but the demonstrated dysfunction of the liver offers a direct cause for its appearance. It should be further noted here that we do not always find changed sugar tolerance with liver dysfunction. That this should be so is to be expected, in view of the large number of wholly divergent causes which produce a picture significant of disturbed liver function. The storage and metabolism of sugar by the liver is but one of its many functions. That some of these may be profoundly disturbed without producing correlative changes in all, is too patent to require discussion. The patient's atrophic testicles play no part in the picture. We have shown that ablation of the testicles in adult years will not affect significantly any of the objective findings of the complete laboratory analysis. The diagnosis on this patient is a current thyroid failure coupled with some measure of liver dysfunction. The physical habitus of the patient reflects an earlier endocrinopathy involving the pituitary which has ceased to be actively operative.

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THE RESULTS OF REPLACEMENT THERAPY IN AN HYPOPHYSECTOMIZED PUPPY: FOUR MONTHS OF TREATMENT WITH DAILY PITUITARY HETEROTRANSPLANTS*

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SAN FRANCISCO

Recent experimental studies on rats, cats and dogs have shown conclusively that the hypophysis is not essential to life in these animals, and although its removal is accompanied by remarkable physical changes resulting primarily from retarded development, and that although their span of life after hypophysectomy may be shorter than that of the control, it is of sufficient length to indicate that the removal of the pituitary has not resulted in death.

Aschner (1) in 1912 published striking photographs of hypophysectomized puppies of various ages which had remained infantile in appearance and size until sacrificed. Using the buccal approach, his hypophysectomies were performed as early as the eighth week of life and the animals lived for months.

The intracranial approach devised by Dandy and Reichert (2) has made possible a successful and complete hypophysectomy in puppies as early as the third week of life. This procedure is facilitated by the preoperative intravenous injection of a hypertonic solution of sodium chloride to shrink the brain.

Evans and Long (3) have found that fresh anterior lobe fluid will produce gigantism if given intraperitoneally to immature rats. This extract was found to stimulate hypophysectomized rats to normal growth but failed to affect their sex glands.

Putnam, Teel and Benedict (4) have just reported the use of an anterior lobe extract in a young bull dog over a period of eight months with progressive gain in weight above that of its littermate control. They also state that in preliminary ex-

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periments a restoration of growth was brought about in hypophysectomized dogs and rats.

The negative results of transplantation experiments in dogs may be attributed to the inappreciable effect of the absorption of a single transplant.

Smith (5), using daily transplants of the fresh pituitary gland of rats, was able completely or in large measure to overcome the disabilities caused by hypophysectomy in immature rats. This replacement therapy led to a restoration of the normal rate of growth, induced the normal function and corresponding histological appearance in the sex organs and led to a reparative phenomena in the atrophied thyroid and suprarenal cortex. Smith and Engle (6) were able to induce pre-

Fig. 1. Littermate females, 6 weeks old and just before hypophysectomy on 16. 16, wt. 2.76 kgm.—17, wt. 2.5 kgm.

cocious sexual maturity both in immature and in hypophysectomized rats, in two animals within thirty-six hours, by their fresh daily transplants.

The illuminating results obtained by Smith and Engle (7) with daily hypophyseal homeo- and hetero-transplants in mice and rats suggested an investigation of the effect of daily injec-

tions of fresh rabbit pituitary gland in an hypophysectomized puppy.

Replacement therapy was begun in a female puppy which had had a total hypophysectomy when six weeks old. At the time of operation the base of the brain in the infundibular region was cauterized by heat to insure complete removal of hypophyseal tissue. This animal was constantly kept with her

Fig. 2. Two months after total hypophysectomy. 16, wt. 4.0 kgm.—17, wt. 5.4 kgm.

littermate control, also female, living out of doors and in the sunshine. Figure 1 shows their appearance just before operation on dog 16. The subsequent photographs and x-rays, Figures 2, 3, 4 and 5, substantiate the fact that after months of observation she remained infantile, failed to grow, retained the puppy face and hair, failed to erupt permanent teeth and ex-

hibited infantile genitalia, further indication that a total hypophysectomy had been accomplished.

Six months after hypophysectomy, when the animal was seven and one-half months old, and when the control had attained adult size (Figures 3, 4 and 5), dog 16 was given fresh whole rabbit's hypophysis every day by the following technic described by Smith and Engle (7). The pituitary gland was quickly exposed and freed under aseptic conditions, finely minced with scissors within the skull and then aspirated into a small glass pipette and injected at once subcutaneously and intramuscularly into the puppy. Definite swelling of the vulva

Fig. 3. Six months after hypophysectomy on 16 and when 7.5 months old. 16, wt. 4.2 kgm.—17, wt. 9.3 kgm, and fully grown. At this time replacement therapy started on 16.

appeared within forty-eight hours and within three days (Figure 6) became so great as to protrude three centimeters from the body. This marked distention of the external genitalia (Figure 11) persisted throughout the four monthts of replacement therapy, while the external genitalia of the control remained normal in size and the animal never came into heat. A

vaginal secretion appeared in dog 16 about two weeks after the beginning of injections but she did not attract a male dog until the eighteenth day, when coitus was attempted, although impregnation was not permitted.

Little is known concerning the time of ossification of the epiphyseal lines in the dog. Skeletal growth was therefore

Fig. 4. X-ray photograph of head of operative animal and littermate control when 7.5 months old and 6 months after hypophysectomy. Milk teeth still present in 16, whereas permanent teeth in 17 appeared in fifth month.

carefully followed by frequent x-ray studies of the entire body and in particular of the long bones taken at six feet distance and always in the same position. These x-ray plates showed that for the two and one-half months after reaching the age of five months the proximal and distal epiphyses of both the femur

and tibia remained open in both dog 16 and in the control dog 17. Measurement of the tibia during this period showed an increase of 0.7 cm. in length in dog 16, while the tibia of dog 17 increased 1.9 cm. Injection treatment was instituted at the age of seven and one-half months when the distal epiphysis of the femur in dog 16 was nearly ossified, and open epiphyseal lines remained at the proximal end of the femur and both ends of the tibia. At this time all four epiphyses were practically ossified in the control dog 17, which had now attained full growth (Figure 5).

Fig. 5. X-ray plate of femur and tibia when 7.5 months old and 6 months after hypophysectomy.

For the first two months of injection therapy the tibia of dog 16 increased 1.0 cm., whereas in the control there was no increase in length, a further indication that maturity had been reached in the control when replacement therapy was begun. Measurement of the femur during this same period showed a

growth of 1.0 cm. in dog 16 (Figure 9) and practically no change (0.1 cm.) in dog 17. At the end of this period the distal epiphysis of the femur in dog 16 was completely ossified, with the proximal epiphysis of the femur and distal epiphysis of the tibia nearly closed. At this time, however, all the epiphyses of the tibia and femur were found to be completely ossified in dog 17. Measurement of the skull taken from inion to

Fig. 6. Three days after replacement therapy started on 16, with daily injections of fresh rabbit's whole hypophysis. External genitalia swollen within 48 hours after first injection.

tip of maxilla showed an increase in length for the initial two months of 0.7 cm. in dog 16 (Figure 8), while in dog 17 there was only 0.2 cm. of growth.

At the end of the third month of therapy both epiphyses of the femur in dog 16 were closed and those of the tibia were nearly ossified. At the end of the fourth month the distal

epiphysis of the tibia was closed and the proximal one nearly ossified. Thus during the first two months of replacement therapy the changes in the epiphyseal lines indicated that the puppy was approaching maturity and that this had been attained during the last two months.

Fig. 7. After two months of replacement therapy, when 9.5 months old and 8 months after hypophysectomy. Operated animal fully as active and alert as control. 16, wt. 4.5 kgm.—17, wt. 9.8 kgm.

There was no increase in length of the skull in dog 16 and an increase of only 0.2 cm. in length of each femur and tibia during the last two months of injection treatment.

At the end of four months of replacement therapy in dog 16 the skull had lengthened 0.7 cm., the femur 1.2 cm., the tibia

1.2 cm., while in dog 17, during the same period, the skull had lengthened only 0.2 cm., the femur 0.2 cm., and the tibia 0.3 cm.

The weight of the experimental puppy increased at a little below the normal rate for the first three weeks after hypophy-

Fig. 8. X-ray plate of head of hypophysectomized puppy just before (upper) and 2 months after (lower) replacement therapy to show growth of skull and eruption of permanent teeth.

sectomy, then showed no appreciable gain for a subsequent period of five months. During the four months of replacement therapy a slight increase in weight occurred, as shown by the chart (Figure 12). Adipose tissue, especially in the groin, defi-

nitely disappeared during the first two weeks after beginning the transplants. One factor which may be considered as interfering with a marked gain in weight, such as Smith (5) showed in his immature hypophysectomized rats, whose controls were not fully grown, is that replacement therapy was instituted late

Fig. 9. X-ray plate of right hind limb of hypophysectomized puppy just before (left) and 2 months after (right) replacement therapy, to show increase in length of the femur and tibia of 1 cm. each.

in development when the control had attained full growth. Experiments are now in progress in which replacement therapy was started soon after total hypophysectomy when the control as well as the experimental animal was still immature.

The permanent teeth appeared during the third to fifth month in the control, while the hypophysectomized puppy still

had all of the first denture at the age of seven and one-half months (Figure 4). Within a month after the beginning of the injection therapy these teeth had dropped out and were replaced by the permanent set, which were, however, much smaller than those of the control (Figure 8). In the third week of therapy the soft, downy texture of the coat began to change to a coarser and longer coat of hair.

Fig. 10. At the end of the four months of replacement therapy, when 11.5 months old and 10 months after total hypophysectomy.

Early in the first week of treatment the puppy also showed a marked change in behavior, with increased activity, attentiveness and playfulness. Jealousy and combativeness became marked when put with other animals, and her endurance was nearly that of the control. Her ability to learn the course of tortuous pathways equalled that of her sister.

At the end of four months of replacement therapy portions of the thyroid, adrenal and ovary were removed at operation

from the hypophysectomized puppy and the control for the purpose of comparative histological study. The adrenal of the control was 4 mm. longer and 1.5 to 2 mm. greater in diameter than that of dog 16. On microscopic examination the gland from both animals had a normal cytological appearance with approximately the same relative proportion of the three layers of cortex to the medulla.

Fig. 11. Swelling of external genitalia of dog 16 persisted throughout four months of replacement therapy.

Microscopic sections of the thyroid of dog 16 showed a parenchymatous hyperplasia with cells of the cuboidal type which formed to a depth of two or three layers in many places. In some areas the acini were nearly filled with these cells. The interstitial cells were more abundant than those of the control

and there was an increase in the number and size of the blood vessels throughout the stroma. The colloid appeared normal. In the thyroid of the control the acini were lined with a single layer of cuboidal epithelium. There was no evidence of hyperplasia and the colloid appeared normal.

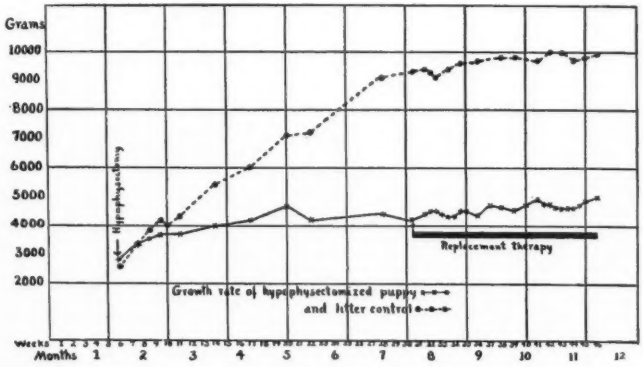

Fig. 12. Chart of the weight of the dogs 16 and 17.

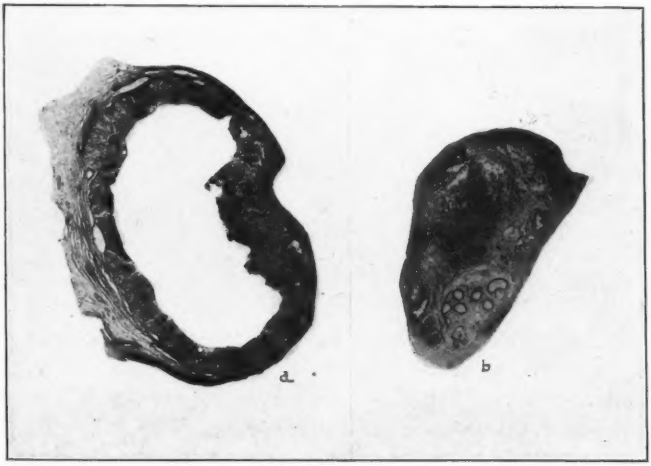

Fig. 13. a. Ovary from hypophysectomized animal four months after replacement therapy, showing cystic corpus luteum. b. Ovary from control animal. Magnification about 4x.

The ovary of the hypophysectomized animal was larger than that of the control and the cornua of the uterus were pink with numerous enlarged and tortuous vessels on the surface. The microscopic sections of the ovary and uterus were studied and described by Dr. C. F. Fluhmann. The ovarian sections of dog 17 were normal, there being numerous primordial follicles in the cortex and several developing Graafian follicles deeper in the substance of the ovary (Figure 13b). There was no evidence of corpus luteum formation.

Fig. 14. a. Endometrium from hypophysectomized animal four months after replacement therapy, showing stage of gland hyperplasia. b. Endometrium from control animal showing resting phase. Magnification about 100x.

Grossly the ovary taken from dog 16 was almost filled by a cystic structure measuring 1.5x1.0 cm. (Figure 13a). The wall was of a grayish white color, with a festooned border and the cyst contained a thick mucoid material. Microscopically the cortex showed normal ovarian tissue with several primordial follicles and one early Graafian follicle. The cyst was lined by a fairly thick convoluted layer of well preserved lutein cells.

The tissue was extremely vascularized but there was no evidence whatever of hemorrhage. The inner lining of the cyst was a thin layer of newly formed granulation tissue.

The cross section of the uterine horn of dog 17 measured 4.25 mm. The endometrium varied from 1.0 to 1.25 mm. in thickness and presented the appearance of the resting phase (Figure 14b). There were comparatively few glands. These were straight and were lined by a low type of cuboidal epithelium which showed no evidence of secretory activity. The stroma was cellular and there were but few blood vessels, although there was an extensive infiltration of free blood attributed by Dr. Reichert to trauma during the operative removal.

The section of the uterine horn of the treated puppy also measured 4.25 mm. in diameter. The endometrium was somewhat thicker than in the control animal and its general appearance conformed to that phase of the cycle referred to by Keller (8) as the stage of gland hyperplasia (the pseudopregnant period of Marshall and Halnan) (Figure 14a). The most striking feature was the tremendous increase in number, size and tortuosity of the glands throughout the whole depth of the endometrium. The individual cells both of the gland and the surface epithelium were of a high cylindrical type and showed evidence of intense secretory activity. The stroma was markedly oedematous and there was a considerable increase in the number of blood vessels but no free extravasation of blood. The myometrium presented no abnormalities.

SUMMARY

The disabilities arising from hypophysectomy in a six weeks old female puppy were in a large measure overcome by four months of replacement therapy with daily fresh heterotransplants of rabbit pituitary.

The puppy remained in a state of oestrus throughout the four months of replacement therapy, although the control never came into heat.

Failure to obtain marked increase in growth and weight in this experimental animal can be attributed to the fact that replacement therapy was instituted at the stage of life when the control had attained full growth.

Experiments are now in progress in which replacement treatment was started soon after total hypophysectomy when the control as well as the experimental animal were still immature.

I want to acknowledge the devoted care and attention given these animals by Ludwig Rübig and John Kratsch, and to express my appreciation of the excellent photographic work of W. J. Taylor.

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THE ROUTE OF ABSORPTION OF THE ACTIVE PRINCIPLES OF THE POSTERIOR HYPOPHYSIAL LOBE

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- Oxytocic titration
  - Apparatus
  - Guinea pigs
  - Solutions
  - Procedure
  - Interpretation
  - Calculation
- Melanophore titration
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INTRODUCTION

In 1910 Cushing and Goetsch (12) showed that human hydrocephalic cerebrospinal fluid, when concentrated twenty-fold on a waterbath and injected intravenously into an anaesthetized rabbit or dog, gave pressor and other responses not dissimilar to those of aqueous extracts of the fresh posterior hypophysial lobe. They therefore postulated on a physiological basis

a route of absorption for the principle which had earlier been advanced by Herring (25) on histological grounds, i.e., the principle elaborated by the pars intermedia passes into, and is possibly activated by, the posterior lobe, whence it streams as particulate hyaline matter up through the infundibular stalk into the cerebrospinal fluid of the third ventricle, and is thence absorbed by the blood stream into the body; this may be designated an indirect or transneural route. The validity of the specific physiological responses upon which this postulation was based was questioned by Carlson and Martin (9), and subsequently Jacobson (28) showed that analogous concentrates of artificial spinal fluids made up solely of inorganic salts could duplicate the cardiovascular and diuretic effects obtained by Cushing and Goetsch. Later, hower, with the advent of the oxytocic method, numerous investigators (10, 46, 36, 29, 35) reported the presence of an ecbolic substance in the cisternal and ventricular (but not spinal) fluid of all mammalia investigated.*

In 1922 Maurer and Lewis (34), on the other hand, postulated a purely vascular route of absorption for the active principle, largely on negative and philosophic grounds. Histologically, a vascular route for presumably evident *anterior* lobe secretion (19, 39) is as firmly supported as is the transneural route for *posterior* lobe secretion. Hogben (26) in the meantime demonstrated (in 1923) that posterior lobe secretion is blood-borne in amphibia, and Krogh (32), with the advent of his anuran melanophore preparation, that presumptive pituitrin is present in greater concentration in equine serum than in equine cerebrospinal fluid. However, he arrived at an apparent impasse to the extension of the method in the allergic reactions of anuran vascular systems to foreign sera. This difficulty, as well as the allergic response of the oxytocic preparation to serum proteins, has been overcome in the present work by utilizing Smith and McCloskey's (43) observation that pituitrin dialyses readily.

Partition of presumptive pituitrin from serum proteins, and biotitration of the active substance in resulting dialysates, has been the basic method used in the investigation reported below.

*The problem was attacked by Dr. S. C. Harvey in this laboratory in 1915, but the technic of the oxytocic method had not then been dependably standardized and his results were not published.

Normal human, bovine, and canine blood (and cerebrospinal fluid) has been utilized, as well as that of dogs with experimental lesions, and of those showing spontaneous pathological deviations from normal. Identity of the active substance in the dialysates has been conjectured through changes after hypophysectomy, and the probable route of absorption indicated by changes after physiological isolation of the supra-infundibular cerebral ventricle. For titration both the melanophore preparation (37) and the oxytocic method have largely been used.

METHODS

Only final methods used are given; preliminary work and failures are occasionally indicated in Results.

DIALYSING MEMBRANES (22): About 20 cc. of a 6 per cent solution of dry Mallinckrodt pyroxylin in a 15 to 85 (by weight) mixture of absolute ethyl alcohol and Mallinckrodt anaesthetic ether (4 per cent water and alcohol content) was poured into a heavy dry 30 cc. test tube. The tube was then inverted and allowed to drain for 30 to 45 seconds into the stock bottle, while being rotated with its mouth just immersed in the ether vapor filling the bottle above the solution. A strong draft of air was then drawn deeply into the tip of the inverted, slanted, and rotated tube for 60 seconds; this was conveniently accom-

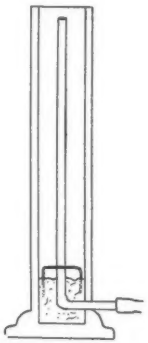

Fig. 1. Convenient air suction tower for making dialysing membranes without blemishes; semi-diagrammatic cross-section. A wooden casing (container for Esbach albuminometer tube may be used) incloses a glass tube embedded in a plaster of paris base. Two wires are so embedded that the test tube mold cannot touch the plaster, insuring good airway.

plished by the device shown in Fig. 1, without spoiling the membrane. The tube was quickly and gently filled to the brim with water for 2 minutes; inverted; the top of the tube reamed with the edge of a forceps to free the membrane at its lips, and the membrane withdrawn by gentle traction. It was occasionally necessary to introduce a

few mils of water between the membrane and the tube to facilitate separation. The membrane was filled with distilled water and immersed in a large jar of distilled water, where it remained for 16 to 24 hours before use.

Opaque white spots on these membranes are microscopically sieves, caused by too thick a layer of collodion; and their presence below the neck of the membrane obviously makes the dialysing sac unfit for use. If the tube used as a mold has blemishes on its inner surface, tiny pin-like holes are pulled in the membrane as it separates. The tube mold finally found satisfactory should be marked legibly and used for nothing else. The permeability of the membranes decreases: (1) with increase in the ether percentage; (2) with duration of air drying; and (3), to some slight extent, with the strength of the collodion. Collodion membrane molds of 250 mil and 500 mil Erlenmeyer flasks are made similarly.

DIALYSIS: The fresh clotted blood samples were centrifuged 20 minutes at 1000 r. p. m. The serum was pipetted off into empty dialysing sacs, where the volume obtained was measured by displacement. The sack was then immersed in a dialysing chamber containing two volumes of fresh mammalian Ringer-Locke solution; with the cylindrical graduates used herein, this sufficed to bring the Ringer-Locke to the level of the serum. The labelled chamber was placed in a refrigerator for eight hours. The rare presence of small amounts either of erythrocytes or of laked blood in the serum does not particularly matter, though the presence of much of the latter seems at times to be the concomitant of detectable histamin contamination. Sacs were removed, and the solution warmed and gently agitated just prior to oxytocic titration. If for any reason dialysis was continued longer than 24 hours, Ringer-Locke solution lacking glucose and bicarbonate was utilized. Cerebrospinal fluid, because of its low protein content, was not dialysed before testing.

OXYTOCIC TITRATION (7, 44, 48): *Apparatus:* A 25 cc. hard glass chamber, immersed in a large water bath maintained at 37.5° C., was arranged to fill (or to empty) at will with warmed Ringer-Locke solution oxygenated through a glass tube having a pore of exit opposite a glass prong on which was impaled the isthmial end of half of a guinea pig bicornuate uterus (Fig. 2). A second similarly accoutred chamber was used in the same bath, so that the other half of the uterus could be utilized constantly to check results of the first. The chambers were encircled with rubber bands to mark the 15 cc., 20 cc., and 25 cc. levels. With the 25 cc. chambers necessary to avoid undue dilution of "unknowns," the unwieldy, expensive, and elaborate tanks used in standardizing pituitrin become unnecessary; casual knowledge of laboratory glass blowing will enable one to assemble for a few cents the simple apparatus depicted. Oxygen was bubbled through a 2 per cent aqueous solution of sodium bicarbonate before delivery into the titration chamber, in accord with the suggestion of Smith and McCloskey.

Guinea Pigs: Virgin guinea pigs, raised segregated from males, when about 225 to 250 grams in weight, yielded satisfactory uteri. Even so, those in rut, with swollen pink vulvae or turgid injected uteri were rejected, for these were hyperirritable and gave preparations of such spontaneous fluctuations in tonus as to make interpretation of results difficult or impossible.

Solutions: This modification of mammalian Ringer-Locke (pH 8.3) was used: NaCl 9.0 gm; KCl 0.42 gm.; $CaCl_2$ 0.24 gm; $MgCl_2$

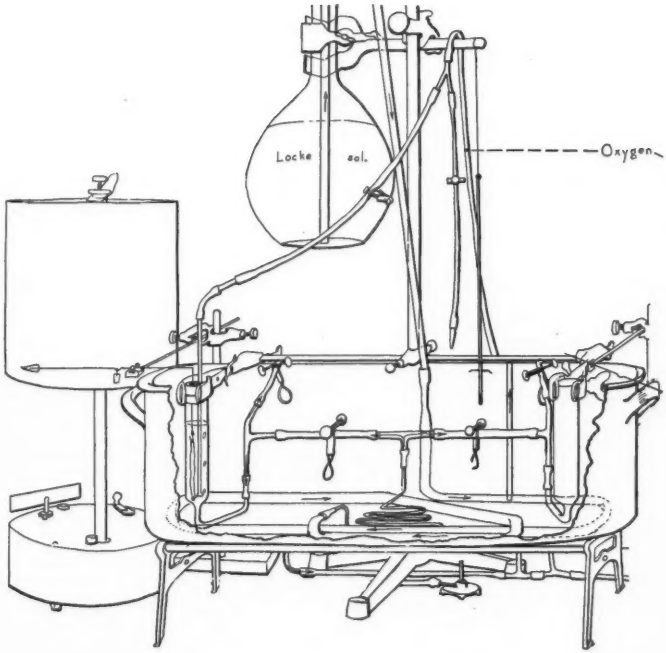

Fig 2. Simple and satisfactory oxytocic titration apparatus. A large fish kettle filled with tap water is raised on a stand and heated by a micro-Bunsen burner; a thermometer is suspended in the bath. The 25 cc. hard glass titration chambers at either end of the bath are made of filter tubes. These are fed with Ringer-Locke solution by gravity through the large-bore glass warming coils at the bottom of the tank; a smaller bore coil may be added as a hydrostatic brake, if desired; access of the fluid to the titrating chamber is controlled by a pinch cock. A second pinch cock is on a tube leading over the back of the tank to a main whose end, dependent over the table edge, forms a second or evacuating siphon; it is convenient to include as a tap on the main a siphon for emptying the large tank itself, as shown. The rod supporting the oxytocic preparation in the titration chamber is hollow; its lower end is drawn out into two prongs opposite one another; one having a slight downward angulation is used to impale the isthmial end of a guinea pig uterus (this prong *must* be of glass); the other is filed off to allow a small orifice for escape of oxygen. The opening in the rubber stopper should be as large as possible, to allow introduction of samples by pipettes. The oxygen is bubbled through a 2 per cent aqueous solution of sodium bicarbonate in a Wolfe bottle (not shown—behind tank) before delivery to the titration chamber. For illustration, the left hand titration chamber only is connected as for use.

0.005 gm.; $NaHCO_3$ 0.5 gm.; dextrose 0.5 gm.; distilled water 1000 cc.; the first five were made up in 20-fold concentration, the bicarbonate being added in solution last, with constant stirring. It was filtered through paper after two hours. The dextrose was added to each fresh dilution from stock. The pituitrin standard was a 0.1 per cent extract of Smith and McCloskey's (42) infundibular powder in 0.25 per cent acetic acid; the powder was brought to a rapid one minute boil in a sterile beaker, filtered sterilely, sealed sterilely in 2 cc. hard glass ampoules, and stored in a refrigerator until used. The powder used was obtained commercially from the Lederle Laboratories, but was checked by oxytocic methods in this laboratory against a standard sample obtained from and through the courtesy of the U. S. Hygienic Laboratory. The histamin was a 0.1 per cent aqueous solution of Burroughs & Wellcome ergamine acid phosphate, made and sealed with sterile precautions in 2 cc. hard glass ampoules, and stored in a refrigerator. Fresh dilutions of standards were made for each titration, with Luer syringes and serological pipettes.

Procedure: The large bath was filled with water at 38° C., and the micro-Bunsen burner lighted; temperature equilibrium at 37.5° C. to 0.1° or 0.15° was obtained in about an hour. A guinea pig was weighed, killed by a blow back of the occiput, stretched on a dissecting board, its ventral coat moistened with water, and the abdomen opened. The uterus was identified, one horn picked up at its junction with the salpynx, the broad ligament cut with scissors close to the uterus, the isthmus split down to just above the cervix, and the lateral half removed. Without shifting the forceps at the uterosalpyngial junction, a pin hook was passed through this extremity (muscle lever thread being already tied in place on the hook), the muscle laid on a thin pad of gauze, its isthmial end impaled on the glass prong of the titration chamber unit, transferred at once to fresh, warm Ringer-Locke solution in the chamber, and attached to the muscle lever, where a 1 gram counterweight was placed 1.5 cm. from the fulcrum. The specimen was thus placed in the chamber with a minimum of handling and trauma. The remaining half of the uterus was quickly mounted in the other chamber, both being in place within 3 to 4 minutes of the death of the guinea pig. A slow steam of oxygen was admitted to the chamber. Thirty minutes was allowed to overcome the initial irritability of the uterus.

It was then washed, and 1000 to 2000 μmgm. (0.1-0.2 mil of 1:50 dilution) pituitrin was introduced into the 20 cc. chamber. The uterus reached its full contraction in 3 minutes; the kymograph was then stopped, the uterus washed, and 7 minutes allowed for relaxation. Several contractions with known amounts of pituitrin in varying quantities were recorded in each chamber, while a graduate of unknown was allowed to warm in the large bath. Five or 10 mils of an unknown were now introduced with a warmed pipette into a 15 cc chamber (the 20 cc. chamber, just large enough to immerse the preparation completely, was drained of 5 cc. the instant before the unknown was added), and a 3-minute contraction curve recorded; the uterus was again washed, and had relaxed for the next titration in 7 minutes. The time intervals adopted were always followed consistently throughout a titration. After 5 or 6 unknowns were titrated, the uterus was restandardized with known pituitrin, and further unknowns assayed; the series always ended with a restandardization. With this method, and these solutions (pH 8.3), the response of the uterus became erratic, if ever, in the 5th or 6th hour of titration; when this happened it was discarded.

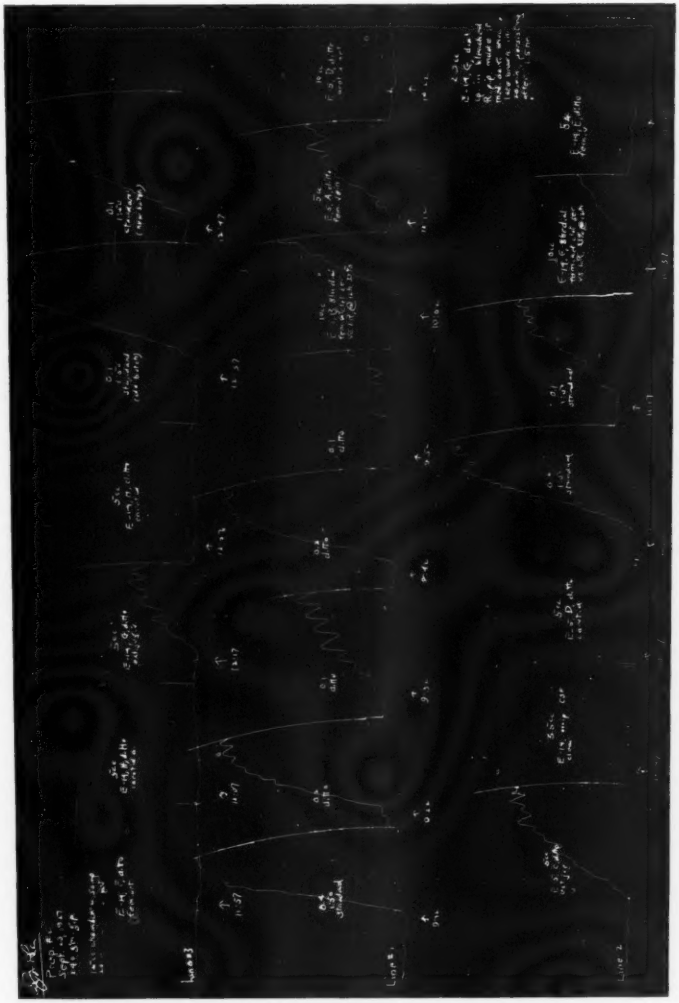

Fig. 3. Sample record of an oxytocic titration. Method of intepretation and calculation from such a record is detailed in the text.

Interpretation: The uterus of a virgin guinea pig responds with identical contractions to identical successive doses of pituitrin (15, 16): within certain limits, it also responds quantitatively to varied doses (44). The bulk of use of the oxytocic preparation has been for biological assay and standardization of posterior lobe extracts, where slightly submaximal contractions are used and striven for; this type of curve is well known in the literature. Very small doses of commercial pituitary extracts (Parke-Davis; Armour), or of standard pituitary powder extract, or of weakly acid extracts of fresh posterior lobe (see Discussion), however, produced changes in tonus which are not so familiar (46), which are not so exquisitely quantitative, and whose variations are more labile when standard conditions are not strictly observed. The sensitivity of a good preparation varies slowly throughout a titration, until after a lapse of hours it may eventuate in a spontaneous irritability such as to make the uterus unfit for use. In assigning a recorded numerical value to the height of a contraction produced by an unknown substance, not only must the rise be interpolated with good judgment between successive standardizations of the uterus, but results obtained from each of the two preparations be considered. One-half of a titration record is shown in Fig. 3. Initial response to introduction of a dialysate after pituitrin, or of pituitrin after dialysates, may be exaggerated. To aid in interpretation therefore it is well to introduce Unknown A first to Preparation 1, followed in sequence by Unknown B, etc.; while Unknown B should be introduced first to Preparation 2, and followed by Unknown A, C, etc.; and it is always well to give two or more doses of pituitrin in restandardization. The qualitative variations in the series of unknowns is furthermore checked by the simultaneously run melanophore biotitration mentioned below.

Calculation: Example: (Fig. 3, line 1, 10:12 p. m.) Thirteen mils of Dog E-5's serum from a clot of femoral vein blood was dialysed for 8 hours against 26 cc. of Ringer-Locke solution, resulting therefore in a 33 per cent dispersion of the dialysable substances at equilibrium. An osmotic rise of the serum in the sac does not interfere with concentrations, since dispersion of dialysable substances is uniform at equilibrium, and only initial volumes need be considered. Five mils of this dialysate, when added to 15 cc. of liquid bathing the uterus, produced 4/5 as high a contraction as the 9:32 and 11:17 titrations (the 9:52 contraction is ignored on the basis of the antecedent three contractions). Since each of these latter was a response to pituitrin in 100 μmgm./mil concentration (0.1 cc. of 1:50 dilution of a 0.1 per cent extract of the powder, in a 20 mil titration chamber), the value of the 10:12 curve is 80 μmgm. However, the 33 per cent sample was further diluted to quarter that strength through introduction into the Ringer-Locke of the chamber, and the ultimate dilution is one-twelfth (33 per cent x ¼), and the curve represents five-twelfths (5 cc.) of the initial serum's strength, or 180 μmgm.

MELANOPHORE TITRATION (37): Krogh's frog perfusion preparation has been used as companion to the oxytocic method to confirm qualitative variations in series of unknowns. In preliminary work it did yeoman service in detecting gross contamination with histamin far below the delicacy of chemical color tests [1000 μmgm. (31)].

OPERATIONS: *Samples:* Bloods for titration were collected by aseptic exposure of the vessels under local anaesthesia (1 per cent novocain infiltration: no adrenalin), for eight months of the work; the procedure was quiet, the animals unexcited and docile throughout.

In the experiments of the first six weeks, however, the animal was anaesthetized with intravenous chloralose; external and internal jugular veins, carotid artery, femoral vein and artery, and endothelial wall of torcular Herophili, were exposed; the following day these now painless wounds were reopened aseptically and blood collected, also without excitement. This, however, was abandoned as containing more departures from normal than did quiet collection under novocain. Canine cerebrospinal fluid was uniformly obtained by cisternal puncture through the occipito-atlantoid ligament, the head being in moderate anterior flexion.

Hypophysectomy: A few hypophysectomies were done by the classical temporal route (11), but the majority by a transbuccal procedure described elsewhere (38).

Sequestration of cerebrospinal fluid from the third ventricle: To block the normal route of flow, the aqueduct of Sylvius was occluded by depositing accurately in it a gelatine shell inclosing iodized cotton (18) by a low cerebellar approach just above the occipito-atlantoid ligament. To avoid probability of ependymal and intraventricular venous absorption, the vena magna Galeni was occluded by two silver clips (13) just posterior to the two vena parvae Galeni (18). In one dog a bilateral lateral choroid plexectomy in addition was done (18), in an endeavor to avoid possibility of retrograde absorption through the plexus itself (23).

NECROPSIES: The brains of the two dogs with "sequestered" third ventricles were fixed preliminarily by injection of formalin into the carotids, and the entire decapitated head fixed for two weeks in formalin before the brain was removed and sliced into 5 mm. coronal sections. The hypothalamic regions of hypophysectomized dogs were removed en bloc with contiguous leptomeninges and dura, without disturbing relations. These were fixed in Zenker's fluid and completely sectioned serially at ten microns from chiasm to corpora mammalaria, and each section examined microscopically after staining with haematoxylin and eosin.

UNITS (37): Both Krogh units and metric μmgm. (micromilligram) are used in reporting results. Krogh (32) has previously used as an experimental unit 0.5 mgm. of international pituitary powder in a cubic meter of water. The reporting of such accurate, but infinitesimal, amounts involves either bewildering arrays of ciphers or cumbersome powers. The convenient metric micromilligram ($1x10^{-9}$) is therefore used herein in reporting results in terms of international pituitary power.

RESULTS

NORMAL DOGS: *General:* Dialysing sacs made of parchment allowed passage of presumptive pituitrin at much slower rate than those of collodion made as described above. Even after 48 hours of dialysis equilibrium had not been reached. Six per cent collodion membranes in 50-50 alcohol-ether were too permeable, and after 36-54 hours allowed laked haemoglobin when present to pass through. Double-dipped 4 per cent collodion 50-50 alcohol-ether membranes were satisfactory, but uselessly

hard to make. The 6 per cent 15-85 alcohol-ether membranes were uniformly adequate; after 8 hours in the dialysing chamber, serum and dialysate turned the skin of a frog perfusion preparation to same shades of color; longer dialysation did not detectibly increase the percentage of active substance in the dialysate. The use of small test tube brushes as whips for defibrinating blood, caused gross contamination with histamin; German silver wire whips were found satisfactory. In other early instances, contamination with histamin seemed to parallel roughly the degree of laking; the presence of histamin was deemed indicated by an abnormally high oxytocic titre in the face of blanching of the melanophore preparation.

Distribution: Bloods of thirteen normal dogs showed constantly presumptive pituitrin in concentration ranging from 75 to 360 μmgm. per mil, as measured by the oxytocic method. Five of these studied in detail showed concentrations in different vascular channels similar to those of Blood No. 8 from an exuberant male Airdale weighing 20 kgm.: external jugular vein 180 μmgm.; carotid artery 120 μmgm.; cisternal cerebrospinal fluid 120 μmgm.; femoral vein 70 μmgm.; torcular Herophili 360 μmgm. Three of these animals, however, showed smaller concentrations in the torcular (62, 75, 90 μmgm.) than in the external jugular vein (180, 120, 200 μmgm.). Blood in the small internal jugular of the dog had the same titre as the external jugular; the femoral artery carried more than the vein. That is, either torcular or jugular led, next in sequence was arterial blood and cerebrospinal fluid, and finally the lowest titres were obtained in the femoral vein. These qualitative differences were confirmed on the frog perfusion preparation.

Transport: Defibrinated blood serum was found to have slightly less presumptive pituitrin (120, 225, 150 μmgm.) than blood clot serum (140, 270, 165 μmgm.). The amount found in the erythrocyte residue after centrifugation of defibrinated blood was found to vary from 30 μmgm. to nothing, depending on the thoroughness of separation from serum. The amount found per unit of defibrinated whole blood was less than in defibrinated blood serum, probably due to inclusion of corpuscular volume in the whole blood. The amount found in the dialysate of whole blood allowed to clot in the dialysing sac,

either with collodion membranes (8 to 24 hour dialysis) or parchment (24 to 48 hours), was always small, probably due to mechanical interference with diffusion currents. These differences were confirmed qualitatively on the frog perfusion preparation. The detectible substance is therefore carried in the plasma, and greatest yield is obtained when the contracting clot is allowed or helped to express its own serum.

PATHOLOGICAL BLOODS: One dog which developed a furious erysipeloid infection of the dorsal snout 36 hours after a chloralose transtemporal operation was found at the 74th hour to be wholly without detectible presumptive pituitrin in blood or cerebrospinal fluid, either by frog or uterus method. A dog in extremis from meningitis was also found to be without detectible pituitrin.

A female Collie jumped as torcular blood was being collected; the needle passed through the sinus to the ventral bony plate of the skull; and although the dog appeared normal afterward, the bloods collected were found inactive on guinea pig uterus, and turned frogs' skin a peculiar shade of green not elsewhere encountered.

Successive samples taken from the external jugular during exsanguination have shown minor depressions of oxytocic activity, but the interpretation of this is obscure, inasmuch as the then increasing coagulability of the blood might indicate an epinephrin inundation. Epinephrin inhibits guinea pig uterine tonus. Whatever the cause, it was not sufficient to interfere perceptibly with qualitative relations in the frog perfusion preparation.

In a single instance, blood of an exsanguinated dog was found to be wholly inactive on guinea pig uterus, after standing as a dialysate (pH 8.3) for 54 hours, although this same dialysate was active on a frog perfusion preparation and showed enough unmistakable variation to allow interpretation of distribution of the active principle between corpuscles, sera, and whole blood; the possible significance of this is touched on below.

A dog which had lost about 33 per cent of its weight while being "starved" for five weeks by only occasional gavage with glucose, with daily doses of morphia, was found to have a low normal concentration presumptive pituitrin and a normal distri-

bution[1], while one which had lost about 50 per cent of its weight had a low concentration and an almost uniform distribution[1]. Both dogs fourteen days after resumption of feeding and discontinuance of morphia showed astoundingly high titres[2], but after each gaining 25 per cent in weight in the following two weeks returned to normal concentration and distribution[3].

OPERATIVE EXPERIMENTS: *Third ventricle sequestration:* An 18 kgm. female Collie and a 21 kgm. male Airdale each had a silver clip ligation of the vena magna Galeni 4 to 5 mm. anterior to the splenium; titration ten days later showed normal concentration and distribution of presumptive pituitrin. The iter was then occluded in both. Seven to ten days later they became irritable, relaxed, negativistic, idiotic in behavior, showed evident impairment of vision and had over 1.5 diopters elevation of the optic discs, deep pressure on abdomen or jugulars produced no acceleration in rate of flow from cisternal puncture needle. One (male) now showed no substantial alteration in the distribution formula[4], while the other showed not only an elevation of the entire level of the curve, but also a reversal of the customary femoral artery-femoral vein ratio so frequently found later[5]; both, however, showed higher concentrations in the external jugular than in cisternal cerebrospinal fluid, and no lowering of presumptive pituitrin after ten days of "sequestration" of the third ventricle. The male was necropsied six days later, after another titration with similar findings; the clip was found tightly closed, and the iter plugged; the ventricles were somewhat dilated. A titration done on the female three weeks after occlusion of the iter showed

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Concentration of active substance in μmgm. per mil of serum in:

	External Jugular Vein	Carotid Artery	Femoral Artery	Femoral Vein	Cerebrospinal Fluid
1.	115	38	118	150	90
	72	72	72	72	5
2.	1950	1400	1900	1300	240
	1500	700	1500	1160	120
3.	185	25	25	62	20
	150	100	100	125	10
4.	112	35	35	18	75
5.	840	740	520	720	720
6.	192	192	120	168	100 cis
					100 lat
7.	18	18	18	150	8
8.	130	70	90	150	60
	375	75	375	600	16
9.	88	88	88	88	60
	5	5	54	54	144 yellow

that the active substance had fallen to normal levels, and that cerebrospinal fluids from the cisterna and from the lateral ventricle were of equal concentration, although less in amount than external jugular[6]. Necropsy three hours later (intracarotid formalin) showed clip and plug in place, dilated iter anterior to plug, moderately dilated third and lateral ventricles, and a flattened Lima-bean shaped pituitary body.

Hypophysectomy: Six female dogs showed, within normal variation, the usual distribution of active substance. Most were given only a single preliminary titration, but one was titrated four times over a period of a month before operation. Four dogs showed the femoral artery-femoral vein inversion discussed below. They all received a transbuccal hypophysectomy, and had a transient mild polyuria for one to three days.* Two to four weeks later some showed nearly complete absence of active principle[7], while others showed either normal amounts or an intensification[8]. These latter, however, during the following month also dropped low[9] by the time others had astonishingly returned to normal. The two that had returned to normal were necropsied, along with one which had totally failed to show a drop. The remaining two developed bad dispositions, moderate obesity, sedateness, frowsy, bushy coats of very slowly growing fine hair, and their subsequent surgical wounds healed with considerable sluggishness; control animals kept under identical conditions did not show such changes. Within three to five months after operation, however, while the somatic changes remained unchanged, the oxytocic titre of their bloods and cerebrospinal fluid slowly returned to normal concentration and distribution. In every titration throughout their entire series, concentration of the active substance in the cerebrospinal fluid was less than in the external jugular vein, and the femoral artery-femoral vein inversion persisted. They were necropsied on the 88th and 152d day.

The 6000 serial sections of the hypothalamic regions of these five dogs were illuminating. The 152-day dog showed bilaterally, one to two mm. from the midline in the post-chiasmal

*The tuber cinereum of one was deliberately injured by a shallow incision 3 mm. long, after an uncomplicated hypophysectomy. The animal had marked polyuria (5-6 liters daily), became comatose after 18 hours, developed a typical "cachexia hypophyseopriva," and died with a rectal temperature of 94° F., at 40 hours.

and pre-infundibular region, a few 60-80μ nests of pars tuberalis cells, which, as one progressed caudad, spread thinly over the inferior surface of the third ventricle as lateral epaulettes as far as the carotid artery, meeting, however, in the midline at the infundibular region, and covering thickly there a flat 0.1x1.0 mm. evagination of the floor of the third ventricle made up solely of neuroglial tissue indistinguishable cytologically from the walls of the ventricle itself (Fig. 4); this nubbin showed no infundibular cleft. After it had disappeared the carpeting of the pars tuberalis continued widely caudad for several millimeters. The 88-day dog was not dissimilar. The two dogs that had had an earlier and less prolonged dip from normal,

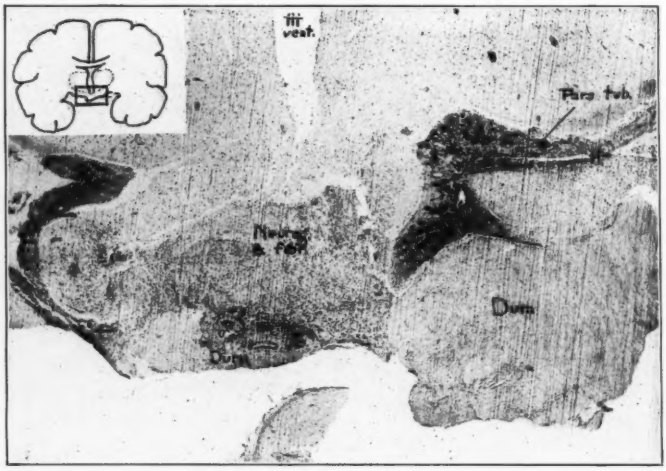

Fig. 4. Photomicrograph of coronal section of Dog E-7's hypothalamic region in neighborhood of scar from removal of anterior and posterior lobes, together with as much hypophysial stalk tissue as possible. Note the neuroglial and fibroblastic reaction above the regenerating dura, and also the still existing lateral epaulettes of pars tuberalis; other sections show still larger amounts of pars tuberalis. The neuroglial tissue immediately underlying the tuberalis cells on the left may be remnant of hypophysial stalk, even though no evidence of hypophysial cleft is found in other sections. The rectangle in the small sketch in the upper left hand corner shows the area enlarged in the photograph.

each showed the same picture, except that rather more (0.2x0.2 x1.1 mm.) of undestroyed posterior lobe (or neuroglial repair) was present; one nubbin showed a definite short infundibular cleft. The dog which had shown no change in titre whatever

was without trace of pars anterior or pars intermedia, had the usual carpeting of the third ventricle by pars tuberalis, and a 1.0x1.0x0.8 mm. piece of stalk left, containing an infundibular cleft surmounted within the third ventricle by a small plug of neuroglial tissue. In this one dog, moreover, was there the sole suggestion of a few wisps of posterior lobe tissue, badly sclerosed and infiltrated, near the posterior adherent vascular attachment of the lobe to the brim of the sella turcica, from whence at operation it is removed with difficulty by curette.

Tissue extracts: Approximately 12 per cent extracts in ¼ per cent acetic acid were made of thalamus, globus pallidus, and tuber cinereum, from five normal dogs. One set of these in 2 cc. ampoules was tried on an oxytocic preparation and all found to be inactive. When the subsequent four sets had been accumulated, however, and combined, the thalamus and pallidus were still found inactive, while the 8.5 cc. of tuber cinereum extract (neutralized to pH 7.4) produced a strong contraction calculated as representing 1100 μmgm. of pituitary powder per gram of substance. A roughly 1 per cent similar extract of canine pars neuralis four hours post-mortem produced curves interpreted as 28 mgm. per gram of substance. That is, posterior lobe contains at least 25,000 times as much active substance per gram as normal tuber cinereum.

Ergothioneine (21, 45): Just as other known organic dialysable substances of normal blood are inactive, so it was found that newly-discovered ergothioneine was inactive on guinea pig uterus in its physiological concentration (60 mgm./100 cc.) as well as twice this; while on the frog it was inactive both in physiological and ten-fold concentration.

Human and bovine blood: Were found to contain presumptive pituitrin, when dialysates were tested qualitatively either by the oxytocic or frog perfusion method. Its repeatedly found concentration in the serum of beeves was 240 μmgm.

Human cerebrospinal fluid: Fluid obtained by lumbar puncture was uniformly inactive (8 specimens), except in one case of arachnoiditis (Foster, Mar. 23) where a 40 per cent concentration in the test bath produced an almost anaphylactic response. Fresh cisternal and ventricular fluid, however, when

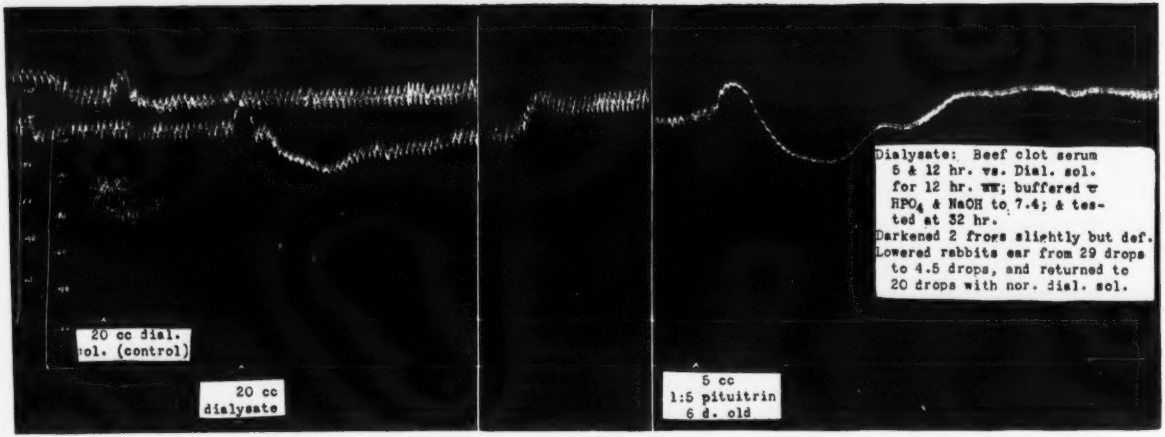
20 cc dial.
sol. (control)
20 cc
dialysate
5 cc
1:5 pituitrin
6 d. old
Dialysate: Beef clot serum
5 & 12 hr. vs. Dial. sol.
for 12 hr. ww; buffered w
HPO4 & NaOH to 7.4; & tes-
ted at 32 hr.
Darkened 2 frogs slightly but def.
Lowered rabbits ear from 29 drops
to 4.5 drops, and returned to
20 drops with nor. dial. sol.

Fig. 5. Haemodynamic action of dialysates of beef clot serum on an amytalized cat. Although there is a considerable depressor action in response to dialysate (about one-third of the duration of depressor action is omitted, for reproduction), the ultimate response is a fairly definite increase in blood-pressure; the dialysate was isotonic with mammalian blood. Dialysing fluid alone produced no response. The records are from the same cat.

obtained from patients without general anaesthesia contained from 25 μmgm. to 240 μmgm. per mil (5 specimens). Ventricular fluid from etherized patients produced either no contraction or else actual inhibition (7 specimens). In one case, fluid was obtained fractionally on three successive days by cisternal or lumbar puncture from the same patient (Gherardi, May 3-5), who had a retarded absorption of cerebrospinal fluid probably due to a thrombosed and canalizing posterior sagittal sinus following extirpation of a parasagittal meningioma; all were abnormal fluids, in that they foamed when bubbled with oxygen in the titrating bath. The first fluid was obtained by lumbar puncture and consisted of four fractions of 32 mils each; they showed respectively 90, 25, 50, and 0 μmgm. per mil. The following day an occipital horn puncture was done, yielding 4 fractions of 22 mils each: 20, 20, 15, and 15 μmgm. per mil. The third day 115 cc. was obtained in 5 fractions by lumbar puncture: 25, 10, 7, 7, and 5 μmgm. per mil. Attempts to store pooled cerebrospinal fluid in refrigerated glass stoppered brown bottles, after acidulation to 0.25 per cent with acetic acid, were unsuccessful, such fluid showing only depressor action after 40 days. Canine cerebrospinal fluid in 50 per cent concentration produced considerable darkening of frog's melanophores, and immersion of an oxytocic preparation in dogs' 100 per cent cerebrospinal fluid effected an assay of 50 μmgm. per mil.

Pressor activity: Warmed unconcentrated fresh beef serum dialysate when introduced intravenously into an amytalized cat produced haemodynamic changes similar to those of pituitary extract, and unlike injections of plain dialysing solution (Fig. 5).

CHEMISTRY

Dialysate: A few miscellaneous color tests were done on the fresh water-clear unsterile dialysates of canine and bovine blood. The membranes used for dialysis were the 6 per cent collodion in 15-85 alcohol-ether, prepared as described above. The biuret test was very faintly positive only on strong alkalization with solid KOH. Saturation in the cold with solid ammonium sulphate produced no demonstrable precipitate in one hour. Half-saturation with phosphotungstic acid, ethyl alcohol,

or picric acid produced a very faint turbidity. Heller and xanthoproteic tests were faintly positive. Ehrlich's diazo reaction gave a flash of pink and red into yellow, and then a slow shading into deep amber; this reaction was not given by pituitary powder extract. Guggenheim's test was negative. While not exhaustive, one may infer from these tests that small amounts of a protein, probably a primary proteose, accompany the active substance of the dialysates.

Attempts at isolation by Abel procedure: Abel (1) has reported a method of isolation yielding 0.175 per cent of impure solid "pituitary tartrate" of high physiological activity from posterior lobe substance. Although realizing that in blood the initial concentration per gram is probably some 200,000 to 1,000,000 less than in the material with which he worked, it was nevertheless hoped that a fraction of a milligram sufficient for physiological demonstration might be obtained from large amounts of sera. This obviously would entail "washtub chemistry" at the start, but it was nevertheless carefully and exactly carried completely through on four samples, 1½ liters of canine serum, and 4000, 4250, and 6000 mils of bovine serum, yielding eventually 82 mgm. of a finely granular tartrate, after 4 treatments with alcoholic picrolonic acid; this, dissolved and reduced to a pH of 7.4 was found to be inactive on guinea pig uterus* and on a frog melanophore preparation. By testing the material at various points in the process, both by melanophore and oxytocic methods, it was found uniformly to be present in detectible quantity until after the second phosphotungstic precipitation.

Concentration: To test the diuretic effect of pituitrin it must be in such high concentration for injection that both a water and a salt diuresis can be excluded. By vacuum distillation at 15 mm. Hg and 20° C., it was possible to concentrate beef serum dialysate (pH 8.3) 30-fold in 8 hours, while increasing its oxytocic activity 6 times per unit volume. This was not carried further, since the inevitable salt concentration obscured the interpretation of diuresis produced.

DISCUSSION

The pertinence of any discussion of route of absorption or excretion of a substance depends first upon recognition and proof of its identity. Chemically, pituitrin is an unknown substance; it has no known specific color reactions other, possibly, than the crude Guggenheim (24) reaction. Physiologically each individual effect of pituitrin may be duplicated by other substances, but the aggregate of its physiological actions (2, 27) is

*"Salt" contraction: a slow, unbroken rise to a plateau, with death of the preparation.

fairly specific. Perhaps the nearest approach to a single delicate and specific test known at present, whether chemical or physiological, is the reversible anuran melanophore reaction; it urgently needs further study, however, particularly with protein split-products.

The substance dealt with in the dialysates appears to be pituitrin because it produces quantitative contractions of the guinea pig uterus, darkens the anuran skin reversibly, produces haemodynamic action similar to pituitrin, is not histamin, has its highest known concentration in the external jugular vein, almost disappears from the blood after "complete hypophysectomy" (discussed below), is increased under presumptive hypophysial stimulation through experimental acute hydrocephalus, and increases markedly after starvation. Against these it may be urged that the present dialysates unquestionably show minimal amounts of probable primary proteose (cerebrospinal fluid also contains traces of protein); and that the guinea pig uterus is the preparation par excellence for study of allergic and anaphylactic phenomena (16). Furthermore, many titrations reported in this paper show active substance unmistakably in higher concentration in the femoral vein than in the femoral artery, leading to warrantable suspicion that one may be dealing not with an endocrine substance but with an unknown metabolite. An item of amphoteric value is that with the dialysing membranes described the active substance is found in substantially equal concentration in mixed arterial and venous bloods of dogs, beeves, and men.

Criteria for experimental hypophysectomy, particularly in relation to such a problem as this, warrant more detailed examination (4) than they have usually received. Just as the diabetes-insipidus-adiposo-genital-dystrophy has been split off (8, 5) from the experimental pituitary deficiency picture (14) and assigned to the tuber cinereum, diabetes insipidus, at least, has recently been rationally reclaimed from the tuber cinereum to the pars tuberalis (3) on anatomical and physiological grounds. In canine hypophysectomy, even by the relatively aneurotraumatic transbuccal route, a wide carpeting of pars tuberalis (Fig. 4) is left on the ventral floor of the third ventricle, together with sufficient infundibular stalk tissue to allow later functional re-

placement of the hormone. If destruction of this tissue is attempted mechanically, chemically, or by electrodesiccation, warrantable objection is made that tuber cinereum injury may have been inflicted. Whether operative dexterity can yet overcome this difficulty remains to be seen. At least the old histological criterion of absence of demonstrable eosinophilic pars anterior cells is no longer a valid criterion of a functionally complete hypophysectomy. All laboratory animals examined have this dorsad pars tuberalis flange; it is present even in Maccacus rhesus

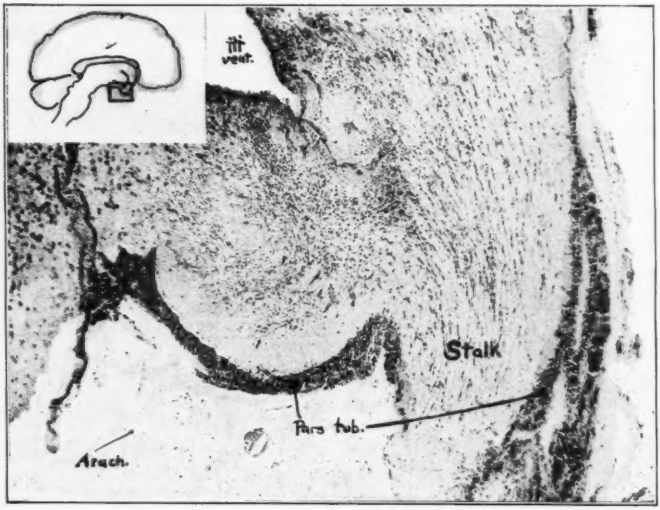

Fig 6. Photomicrograph of sagittal section of infundibular stalk region of Maccacus rhesus, to show that in the monkey, as well as in the dog and cat, pars tuberalis cells are intimately adherent to the floor of the third ventricle and tuber cinerum. The arachnoid is suggested in the section; it is probable that a surgical mechanical removal would not obtain more than is at present missing, and that pars tuberalis cells and a nubbin of stalk tissue would be left. Other sections show that pars tuberalis extends laterally and posteriorly about one millimeter. The rectangle in the small sketch in the upper left hand corner shows the area enlarged in the photograph.

(Fig. 6), although evidently poorly developed in the normal animal. Search of serial sections of the hypophysectomized animals under report fails to show identifiable pars intermedia cells remaining; especial note should be made (25, 34) that presumptive pituitrin returned to normal concentration in blood and cerebrospinal fluid in the demonstrable absence of these cells—which, however, are probably definite secretory organs (33).

The detection of oxytocic activity in extracts of tuber cinereum after "hypophysectomy" has led Abel (2) to postulate an accessory tissue, producing hormone, in the tuber cinereum, but one might, however, with equal justice urge that the activity which he found was due to transneurally migrating hyaline.

Cogent doubt as to the unitarian nature (2, 32) of the active principle has recently been expressed (20, 30). Regular quantitative, and parallel differences in assay of both standard and unknowns were herein found by oxytocic and melanophore methods (37). This might be due to (a) two autacoids, (b) to actions of different parts of one autacoid molecule (32), or (c) to presence of a depressor substance (40) in both standard and unknowns, effective on the melanophore, but not the oxytocic, preparation; this latter hypothetical substance, however, could not be appreciable histamin, since both Pauly and diazo tests on the standard were negative. Mention has been made heretofore of the single instance in which a dialysate, after standing 54 hours in a refrigerator, was found to be inactive on guinea pig's uterus, although exhibiting enough activity on the melanophore preparation to allow apparently accurate qualitative differentiation. Moreover, the type of oxytocic contraction given by acidulated extracts of the fresh lobe, and of the standard powder, differ; the fresh lobe extract apparently may be added until a threshold is reached, and the uterus immediately springs into nearly maximal contraction with only one or two pauses on the up-stroke, while with powder and dialysate the usual type of curve is a less declivatous ascent interrupted by many rapid hesitations (Fig. 3).

If it be granted for the moment that the active substance or substances dealt with in the present paper are the product of the posterior lobe of the hypophysis, a blood-borne, rather than transneural, route of absorption emerges. This is based largely on two findings: (a) the concentration of presumptive pituitrin is always higher in the external jugular vein than elsewhere in the body, while that of cerebrospinal fluid is less than, or approximates, that of arterial blood; (b) after "sequestration" of the third ventricle (third ventricle choroid intact, however), concentrations in blood and cerebrospinal fluid remain unaffected. Against such an idea may be brought: (a) the proved

fact that lumbar cerebrospinal fluid is almost universally found wholly inactive (6, 41) except in parturient women (49) and in the single arachnoiditic fluid reported herewith, while cisternal and ventricular fluids are in contrast invariably active; and (b) that the concentration of presumptive pituitrin is herein frequently found to be greater in the femoral vein than in the femoral artery.

SUMMARY

Quantitative physiological evidence (uterus and melanophore assays) is adduced that presumptive pituitrin is present not only in canine, bovine, and human blood plasma and cerebrospinal fluid, but that it is probably initially absorbed from the gland into the body solely by a vascular route. The detectible substance behaves as if it were at least two entities, is diminished by major infective processes, and starvation, and is increased during anabolic processes.

It is a stimulating debt to acknowledge Dr. Harvey Cushing's constant criticism and suggestion during the progress of this work; it should be added, however, that he is not wholly in accord with the views expressed in the summary above. The kindness of Dr. Stanley Cobb has furnished the Macaque brain, and that of Dr. Blythe Eagles the pure ergothioneine used.

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THE TECHNIC OF GLAND TRANSPLANTATION

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During the past ten years I have contributed many articles on the various effects of gland transplantation. Because of the simplicity of the operation, however, the operative technic was not discussed in detail. Recently, the number of requests received from surgeons from different parts of the country asking for a description of the technic of the transplantation, make it seem desirable to present the subject more fully so that the operation can be performed by others.

In past articles I have taken up "The indications for gland transplantation" and the subject of "Blood grouping between animals and man." I have discussed the kind of individual in whom the gland transplantation is contraindicated, the time and period it takes a transplanted gland to be absorbed, and have gone into detail on the temporary and lasting effects which might be expected. The reader, therefore, who has followed these articles, which have been based on over five hundred gland transplantations personally performed, is in a position to know whether or not he desires to transplant glandular substance from an animal into one of his patients.

In reference to the actual technic, we may take up the details in the following order:

1. The kind of an animal from which to secure gland substance;
2. Age of animal which gives the best results;
3. Methods of securing the gland;
4. Technic of the operation itself;
5. Post-operative care of the patient.

The kind of an animal used for gland transplantation: It is well known that Voronoff prefers to transplant glandular tissue from the anthropoid ape. Others have used glands from goats, and Stanley of California, who adheres to the ram, tried

the human testicle without better results. I have used glands and gland sections from the ram, the sheep, the pregnant cow and the young bull. From my experience with these animals, I prefer the sheep and the ram. Also from experience in transplanting in the human subject, sections of thyroid, sections of prostate, whole ovaries and sections of testicles, and in animals sections of pancreas, I find that sections of testicles and whole and split ovaries give the best results and are less liable to be associated with post-operative sloughing or severe protein reaction.

The age of the animal: There are certain classes of patients, women who have had ovariotomies, and men who have become eunuchs from disease, destruction or removal of their testicles, who do not have very lasting effects from transplantation. These cases require repeated transplantations, and I find that the use of the young animals gives much more lasting results than the use of the gland from the mutton.

Method of securing gland: In my researches the New York laboratorian of Armour & Company has been an invaluable aid, both in selecting the proper kind of an animal and securing healthy glands for transplantation. Anyone deciding to transplant glandular tissue should endeavor to get in touch with a properly qualified laboratorian to assist in this part of the technic, which is very important. Early in my transplantation activities, Dr. Herman Sharlit, associated with the Roosevelt Laboratories, studied with me the cause of necrosis of gland tissue following a transplantation. We came to the conclusion that this frequent necrosis was due to air-borne bacteria. At that time, I had been securing the glands from the animals in a sterilized thermos bottle containing a warm saline solution, relying on after-sterilization of them to destroy any air bacteria that might collect. We found that the glands became necrotic within twenty-four hours and were loaded with air bacteria. I therefore had the technic of obtaining them changed, and they were brought to me from the slaughter house in a sterilized thermos bottle containing a warm glycerine solution. This cut down the percentage of air bacteria 90 per cent. Later the thermos bottle was sterilized and filled with glycerine solution to which ice washed with ether was added. This seemed to

eliminate the air bacteria entirely. Unfortunately, however, glands frequently underwent necrosis. The technic was again altered to that to which I now adhere with very satisfactory results. A thermos bottle is thoroughly sterilized and taken to the slaughter house. The animal is prepared as usual. Blood from one of the carotid arteries is aspirated into the thermos bottle. The glands to be transplanted from this animal are then allowed to sink into the blood. The thermos bottle with its contents is immediately brought to the operating room. The blood is not clotted when it is received. The glands are removed from the bottle and placed in a five per cent solution of acriflavin, which is kept at a temperature of 105° F. for one hour. The patient is on the table with the abdomen sterilized, awaiting operation.

The technic: The technic of the operation for the two sexes is different only as far as the treatment of the gland is concerned. At this point, I should like to repeat a statement that I have made many times before, namely, that the name of *ovarian and testicular transplantation is really a misnomer.* The operator should keep in mind during the entire operation, *that it is a grafting of the skin to the tunics of the ovary or to the tunics of the testicle.* This will better be understood when the next several paragraphs are read.

The transplantation of the ovary will first be described. After novocainizing an area of skin of about three square inches on the abdominal wall with a two per cent solution of novocain containing one cc. of adrenalin chloride to the ounce (I usually transplant in the right or left iliac region), a transverse incision is made across the center of the novocainized area. This incision goes through the skin only and should be about three-fourths of an inch in length. An undercutting knife is then used to make a pocket one and one-half inches square above and one and one-half inches square below this incision, and it should be immediately under the skin; in fact, so close to the skin does the knife adhere that no areolar tissue is left next to the dermis, hence the entire under surface of the dermis comes in direct contact with the gland tunics. One or two ovaries are now removed from the acriflavin solution and are so bi-sected that the organ may be opened like a book. Any blood clot or blood from the wound is next cleared away and a fine ocular needle

threaded with fine silk is passed into the pocket from its upper margin. The needle then passes out of the wound through the tunics of one side of the gland, back again into the pocket, up through the skin and out to the surface of the abdomen. A parallel suture three-quarters of an inch away from the entrance of the first is passed through the skin, out through the pocket and through the tunic of the other side of the gland and back the same way as the first. These two sutures are now pulled by the surgeon holding two pair of sutures within his thumb and index finger. This pulls the gland into one of the pockets of the wound and as they are tied on the surface of the abdomen, the tunics of the gland are sutured to the under surface of the dermis. If the symptoms in the case indicate that two glands should be transplanted, the same procedure is repeated, using the lower pocket. The necessity is emphasized of making these pockets of sufficient size to permit the complete disappearance of the transplanted tissue so that none of it lies immediately beneath the wound. The reason for this is that the gland contains a trypsin-like substance, and if any of the gland tissue lies immediately beneath the incision this enzyme will digest the marginal tissue and keep the wound open for a considerable period of time. The wound is now closed with two subcuticular sutures, a deep subcuticular suture composed of silk and horsehair called "Cutis," and a subcuticular suture going through the epithelium only, of horsehair.

When transplanting testicular tissue, the same area is novocainized. An incision two and one-half inches wide is then made transversely across the top of this area and the pocket extends three inches below the inferior border of the wound and is three inches square. A section of testicular substance two and one-half inches square and about one-quarter of an inch thick is now cut from the lateral surface of a healthy ram's testicle which has been sterilized as detailed in case of the ovary. The tunica externa is stripped from this section, but the remaining tunics are left adherent to the substance of the transplant. This section is now deposited in the pocket, sutured to the under surface of the dermis in the same manner as described for the ovary, and the wound is closed in a similar way.

Post-operative treatment: The patient is allowed to leave the operating room at once and instructed to keep an ice-bag

over the wound for twenty-four hours. If the patient is compelled immediately to resume his occupation, a small elongated ice-bag similar to that which is used in throat cases may be worn beneath the clothing. After the wound has been sutured, the edges are wiped with iodine and alcohol and dusted with a powder of thymol iodide. A small strip of gauze is now placed over the wound and attached to the skin at each end with collodion, care being taken that the collodion does not touch the edges of the wound. The patient is instructed to return each day for observation and dressing. The dressing consists simply in repeating that which is done at the termination of the operation.

The patients usually have a slight febrile reaction from within twenty-four to forty-eight hours. Rarely does this reaction require any attention. In over five hundred cases in my experience only three ran a temperature of over 103° F. In such cases, five grains of aspirin with an ounce of whiskey every three hours, and a colon irrigation seem to be sufficient.

In from four to seven days the sutures may be removed. Several different reactions may be observed. First, the wound may heal by first intention with very little congestion. Second, the wound may become congested and expel some necrosed gland tissue. Seldom, however, does the whole gland undergo necrosis. After this necrotic tissue is expelled, the wound takes two to three weeks to heal on account of delayed fibrosis between the wound edges. Rarely, the whole gland becomes necrotic and is expelled.

The first indications of a successful result of the transplantation is the return of natural vigor. Patients will inform the surgeon that they are sleeping better, that they feel more rested in the morning than formerly, that they feel more like walking and exercising, and that their appetite is markedly improved. Then other indications of general well-being start to manifest themselves, such as return of libido in men, power of erections, more regular bowel movements; the special senses become more acute, and memory as well as mental concentration improves. The blood pressure, blood chemistry and semen, formerly below normal, show a rapid return to normality. The details of the results of gland transplantation I have of course taken up in former articles.

THE ANTIDIURETIC EFFECT OF PITUITARY OXYTOCIC AND PRESSOR PRINCIPLES ON WATER DIURESIS IN MAN

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HANOVER, N. H.

Since Kamm (1) and his co-workers succeeded in separating the extract of the posterior pituitary body into two almost pure fractions, the oxytocic and pressor, renewed interest in the physiology of this organ has been stimulated. These authors observed in rabbits that the diuretic action of pituitary gland extracts was limited to the pressor principle. Gargle et al. (2) studied the effect of the oxytocic and pressor principles on water diuresis in four normal subjects and on thirst and polyuria in two cases of diabetes insipidus. They also found that the antidiuretic effect was possessed by the pressor principle alone.

Recently, I had occasion to observe the effect of the oxytocic and pressor principles of the pituitary gland on water diuresis in a group of healthy adult male medical students. The materials employed were supplied by the manufacturers, Parke, Davis & Company, under their trade names, Oxytocin and Vasopressin.

The water diuresis test consists of the administration of from 500 to 1500 cc. of water by mouth after emptying the urinary bladder, and then the collection, separately, of all the urine excreted at one hour intervals thereafter. Ordinarily, all the water ingested is excreted in four hours. In the experiments recorded below, 1000 cc. of water was administered in each case save for the exceptions noted. In all, twelve subjects served in the experiments. These were divided into three groups of four each. Group I served as control, unmodified water diuresis test. Group II received in addition to the water, orally, 1 cc. (12 units) of oxytocin, intramuscularly, during the course of the water ingestion. Group III received 1 cc. (12-20 units) of vasopressin, intramuscularly, while ingesting

the water assigned to them. Groups I and II experienced no discomfort during the ingestion of water nor during the remainder of the experiment, whereas Group III had in each case difficulty in drinking the full 1000 cc.; only one succeeded in taking the full amount, and he promptly regurgitated 200 cc. The members of this group experienced other discomforts which are recorded below.

CHART I

CONTROL GROUP

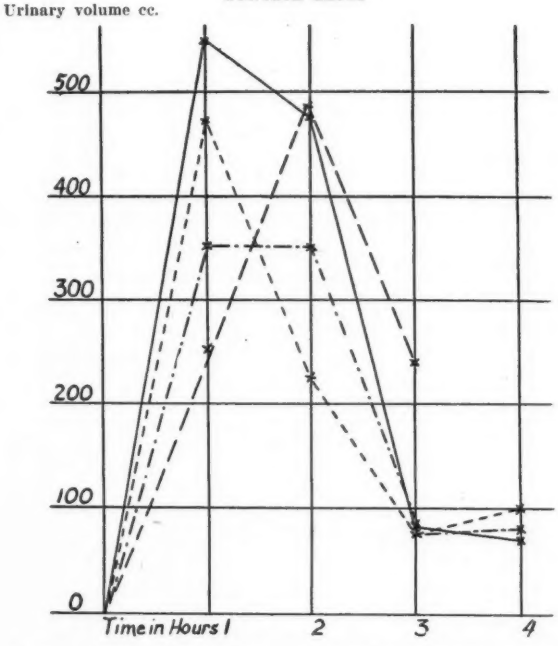

Chart I. Control group. Each member received 1000 cc. of water, orally, and urine specimens were collected hourly. Abscissas, time in hours. Ordinates, volume of urine excreted, in cc.

In order to construct comparative charts for the three groups, the procedure was essentially the same in each case, i. e., all voided before drinking the water assigned to them, all ingested 1000 cc. of water during an interval of 10-15 minutes, save for the exceptions noted; all receiving the pituitary ex-

tracts were injected intramuscularly during the course of the water ingestion; and, with few exceptions, all collected the urine excreted at one hour intervals thereafter. The results obtained in these three groups are recorded in charts I, II, and III, below.

On examination of the three charts, the diuretic effect of water is quite well shown in Chart I; a slight transient retardation of diuresis by oxytocin is demonstrated in Chart II, and a

CHART II

OXYTOCIN GROUP

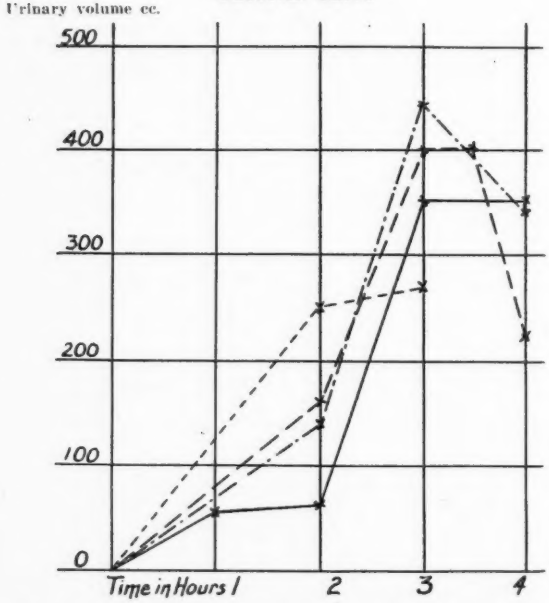

Chart II. Each member received 1000 cc. of water, orally, and 1 cc. (12 units) of oxytocin, intramuscularly. In 3 of the 4 cases here recorded, the first urine collection was two hours after the water ingestion, the other case was one hour after. Abscissas and ordinates as in Chart I.

very distinct and prolonged depression by vasopressin is seen in Chart III. It would seem then that oxytocin has a slight antidiuretic effect. However, in a communication from Dr. Kamm relative to this observation, he calls attention to the fact that the oxytocin supplied has about five per cent of vaso-

pressin as an impurity. This fact can readily explain the result, for he has found that from one to three units of vasopressin have almost as striking an antidiuretic effect as the 12 to 20 units here employed. On this basis, the oxytocin injected contained about a half unit of vasopressin, undoubtedly a large enough quantity to modify the diuresis to the extent observed. From these observations, it is quite clear that the antidiuretic

CHART III

VASOPRESSIN GROUP

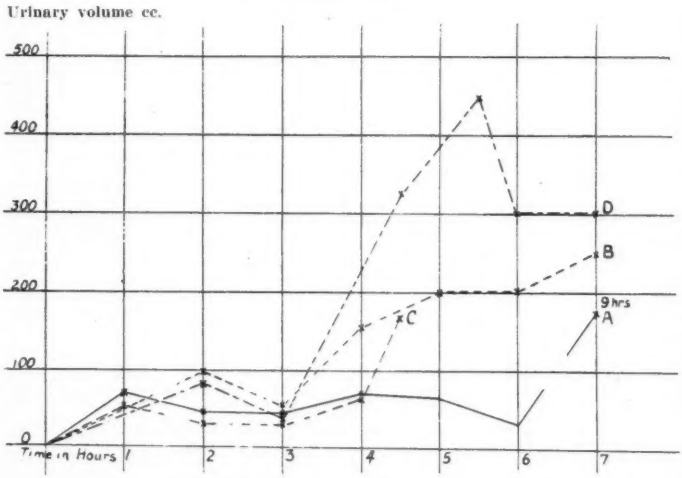

Chart III. A, ingested 800 cc. of water; B, 800 cc.; C, 1000 cc., of which 200 cc. were promptly regurgitated, and D, 725 cc. Each member of this group received in addition 1 cc. (12-20 units) of vasopressin, intramuscularly. A and C voided hourly from the beginning. B and D hourly after the first two hours. Abscissas and ordinates as in Chart I.

action of extracts of the posterior body of the pituitary gland is limited to the pressor fraction. Subject D, in Chart III, shows a diuretic effect following the early antidiuretic effect.

The four control subjects and the four who received oxytocin showed no signs of disturbance due to the tests, and complained of no discomfort. However, the four who received the vasopressin gave evidence of vigorous physiological changes. As mentioned above, one only managed to drink the full amount of water, and he regurgitated 200 cc.; the other three could

not ingest the total amount of water allotted. They all complained of nausea and cramps, and had a prompt bowel movement. These observations point to a stimulation of the smooth musculature of the gastro-intestinal tract as is usually seen after injections of the mixed extract of the posterior lobe of the pituitary gland. These bowel movements were too early to affect the water diuresis tests. All four were very pale for about an hour after the injection.

Vasopressin, then, stimulates the smooth musculature of the gastro-intestinal tract as well as that of the vascular system. The uterus is an organ also composed of smooth muscle, but it responds only feebly to vasopressin and vigorously to oxytocin. Our general conception of the physiological activity of pituitary extract has been that it stimulates all smooth muscle directly. Now, it seems that this conception has to be modified somewhat to explain the reason for the uterus responding in a different manner from other smooth muscles. These observations should serve to open up further experimentation with the object of establishing the mode of action of the extracts of the posterior lobe of the pituitary gland.

SUMMARY

Experiments were made on three groups of four each of healthy young men. It was found that the antidiuretic effect of extracts of the posterior pituitary body is due to the pressor principle.

Whereas the oxytocic principle has a vigorous effect upon the uterine movements, it has little if any action on the smooth muscles of the vascular system and of the gastro-intestinal tract.

Vasopressin is the principle which has a pronounced stimulatory action upon the vascular system and gastro-intestinal tract and but a feeble one on the uterine movements.

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HYPERSENSITIVITY TO INSULIN
A POINT OF DIFFERENCE FROM SYNTHALIN AND GLUKHORMENT

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A married white woman of 41 came to the Diabetic Clinic of The Lankenau Hospital for the relief of distressing occipital headaches preceding and immediately following the menstrual period. These came on, as a rule, in the mornings and lasted several hours. The menstrual cycle was regular each month, lasted five days and was followed by a period of lassitude and weakness.

The patient further complained of an excessive and eccentric appetite, polyuria, with some burning, and also of constipation.

Her past history indicated susceptibility to infections in the upper respiratory tract, causing frequent severe colds, sore throat, and tonsillitis.

The significant features in the physical examination of the patient were moderate obesity (170 pounds), pyorrhea, mild hypertension (184/100) and fasting hyperglycemia of 385 mgm. per 100 cc. of blood. The blood urea was 12 mgm.; cholesterol, 220 mgm. The red cell count showed a mild anemia, the erythrocytes being 3,560,000 and hemoglobin 75 per cent. The leucocyte count was 4,500 with polymorphonuclears, 53; lymphocytes, 40; and large monocytes, 7. Plasma CO_2 was 60 volumes per cent. The Wassermann reaction was negative.

A urine analysis (24 hour specimen) gave a specific gravity of 1.024 and 4.16 per cent glucose. Tests for acetone and diacetic acid were negative.

The patient was given a diet of carbohydrate 70 grams; protein 60 grams; and fat 100 grams; total calories 1420, following a day of starvation. As there was no appreciable effect on the blood sugar after various modifications of the diet, ten

units of insulin three times a day just before meals was prescribed.

Following the first injection of ten units, before breakfast, an erythematous swelling three cm. in diameter developed at the site of injection and the patient complained of weakness, flushes, vertigo, and faintness. Upon reclining for a short time the general symptoms passed away but the local swelling persisted for five days. At noon following another injection of insulin by the nurse the same symptoms reappeared and the attending physician was summoned. A survey of the technique showed a minimal opportunity for factors other than the solution containing insulin to have been the cause of the reaction. Skin sensitization tests using the various preparations of available proteins, including beef and pork, pollens, etc., were made and all proved negative. Four different commercial preparations of insulin were then injected intradermally using one minim of a U-20 strength. Beginning two minutes after injection a blanching bleb appeared at the site of each puncture and gradually enlarged to an area three cm. in diameter. At the end of three hours each reaction had disappeared. Sterile saline was used as control.

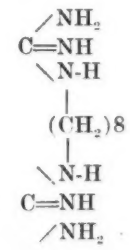
Utilizing the sensitivity of this patient to insulin as a method by which to study possible similarities of insulin, synthalin [of Frank (1) (1a)] and glukhorment [of Von Noorden (2)] an aqueous preparation of synthalin (2.5 mgm. per cc.), and one tablet of glukhorment dissolved in two cc. of phosphate buffer solution, prepared by Dr. Hammett of The Lankenau Hospital Research Institute, further sensitization tests were performed. One minim each of four commercial preparations of insulin (U-20); one minim of aqueous synthalin solution (2.5 mgm. per cc.) and one minim of a phosphate buffer solution of glukhorment (one tablet in 2 cc.) were injected intradermally on the volar surface of the forearm. The glukhorment preparation was controlled by using phosphate buffers pH 8, and pH 6 as controls. Normal saline was again the control solution.

The same reaction once more occurred with insulin as above described; to synthalin there was a very slight blush which faded in two minutes and to the glukhorment preparation no reaction was noted. Blood sugar examinations taken before and after the sensitization tests showed no alteration.

As the present commercial preparations of insulin are now prepared it is unlikely that impurities in the solution would cause the reaction. Joslin (3), Wilder (4), and Geyelin (5) in 1922 reported instances of reaction following injections of the relatively impure preparation, of which at least five cc. had been injected before the disturbance occurred. By refinement in preparation the solutions subsequently marketed contain none of these impurities. On the other hand certain individuals are sensitive even to the insulin as now prepared, if it is given in sufficient amount. In 1926, Walker (6) described a case in which urticaria and edema developed following a week of insulin therapy. Engelberg in 1927 reported a similar type of case. Differing from the case herein described, modification of dosage eliminated further reactions and the patients continued the insulin. Recently Tuft (7) has recorded another case of a patient who became hypersensitive to insulin after several months of insulin therapy. This patient, likewise, showed a generalized rash and swellings of the extremities following insulin.

Abel (8) and his co-workers have found that each unit of insulin contains 0.006 to 0.01 mgm. nitrogen.

In contradistinction to insulin products, synthalin is a synthetic guanidine derivative with the formula:



Glukhorment was originally described as a product obtained by the fermentation of endocrine glands until glycocyanin results. But recent researches by Bischoff, Blatherwick, and Sahyun (9) have shown that glukhorment also contains a guanidine derivative which, they state, "is either synthalin or a near homologue of it."

Note should be made that the patient herein described was

unable to take synthalin orally, suffering from nausea and vomiting each time a tablet was given, a disturbance frequently provoked by this drug. Glukhorment was not given by mouth.

SUMMARY

A brief case report is made of a female patient showing immediate local and systemic reaction to injection of insulin. Comparative intradermal tests with an aqueous solution of synthalin and a phosphate buffered solution of glukhorment gave no local or systemic reaction.

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3. Joslin, E. P. et al. Insulin in hospital and home. J. Metabol. Research, **2**: 651-699 (Nov. & Dec.). 1922.
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5. Geyelin, H. R. Use of insulin in juvenile diabetes. J. Metab. Research, **2**: 767-791 (Nov. & Dec.). 1922.
6. Walker, S. E. Case of diabetes with anaphylaxis following insulin. U. S. Vet. Bur. Med. Bulletin **2**: 700-702 (July). 1926.
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Abstract Department

Influence of suprarenals on blood pressure regulation (Influencia de los glandulas suprarenales sobre la regulacion de la presion arterial). Biasotti, A., Thesis. National Univ. of Buenos Aires. 1927.

The author's aim was to secure experimental evidence under purely physiological conditions and without the perturbing effects of anesthetics and operations. The blood pressures were measured on the femoral artery by the indirect method and with the precaution of avoiding emotional hypertension. Extirpation of one or both of the abdominal chains and the splanchnics was without effect upon the blood pressure. Removal of one adrenal was equally ineffective. If, however, the second adrenal was removed, and the dog died within 20-60 hours, the blood pressure fell rapidly. Removal of one adrenal and demedullation of the other was followed by a hypotension of 3-4 cms., which finally disappeared after 20-30 days. The recovery was not due to proliferation of chromafine bodies nor to the abdominal sympathetic chain. Reactivity to hemorrhage amounting to 1.5 per cent of body weight was found to be much more marked and prolonged (2-5 cms. fall prolonged for three hours) in dogs whose blood pressure had recovered after adrenal demedullation than in controls (1-2 cms. fall that disappeared after an hour). The author concludes that the main role for re-establishing the blood pressure to the normal level corresponds mainly to the vasomotor apparatus, while that of adrenal secretion is only secondary and accessory.—J. J. Izquierdo.

Glutathione and the adrenals (Glandes surrénales et glutathion). Binet, L., and A. Giroud, Compt. rend. Soc. de biol. **98**: 434. 1928.

The adrenal is the tissue of the body containing most glutathione. It is the cortex of the glands which is the richer and in young guinea pigs the zona reticularis, which is the richest part of the cortex in this substance.—J. C. D.

Latent malaria and adrenin (Adrénalino-diagnostic du paludism latent). Canciulesco, M., L. Herman and R. Hirsch, Compt. rend. Soc. de biol. **98**: 459. 1928.

As the result of the study of twelve cases in which 1 to 2 mgm. of adrenalin in a 1 per cent solution was injected subcutaneously, the authors conclude (1) that it is very helpful in diagnosing latent cases since the organism can now be found in the blood, (2) that no untoward results either due to hypertension or to relighting a quiescent malaria follow, (3) that it may be helpful since the organisms are forced out from the security of the spleen into the peripheral blood loaded with quinine.—J. C. D.

Temperature control and the adrenals (Role des capsules surrénales dans la thermorégulation). Chahovitch, X., V. Arnovljevitch and M. Vichnjitch, Compt. rend. Soc. de biol. **98**: 511. 1928.

In normal rabbits injection of milk into the heart was followed by a rise in temperature (rectal). In decapsulated rabbits the temperature fell and the animals died a few hours after the injection.
—J. C. D.

Primary tumor of the suprarenal capsule with especial reference to adrenal virilism. Crosbie, A. H. and L. W. Smith, J. Urol. **19**: 241. 1928.

This is the report of a case in which the tumor was removed at operation.—J. C. D.

The adrenal gland in pregnancy: cortico-medullary relations on albino rat. Donaldson, J. C., Anat. Rec. **38**: 239. 1928.

Measurements by the reconstruction method show that during pregnancy there is no change in the relative volumes of the cortex and the medulla.—Author's Abst.

Adrenal gland in wild gray and albino rat: cortico-medullary relations. Donaldson, J. C., Proc. Soc. Exper. Biol. & Med. **25**: 300. 1928.

Measurements based on the reconstruction method show: (1) The proportion of medullary tissue to cortical tissue is less in the wild gray than the albino, (2) the absolute amount of chromaffin tissue is greater than in the wild gray, and (3) most of the greater mass of the adrenal in the wild gray consists of cortical material.
—Author's Abst.

Comparative sensitiveness of blood pressure and intestinal motility to epinephrin. Dragstedt, C. A. and J. W. Huffman, Proc. Soc. Exper. Biol. & Med. **25**: 241. 1928.

In four dogs to whom neither anesthetics nor drugs were given, a rise of blood pressure without intestinal inhibition in response to epinephrin was observed. Simultaneous records were also obtained

in 6 animals to whom morphine was administered, and in 1 animal to whom paraldehyde had been given. In each of the animals a rise of blood pressure without intestinal inhibition was obtained. Epinephrin was injected intravenously by means of a Woodyatt pump for two to ten minutes. In every instance a sufficient dose of epinephrin was effective in maintaining intestinal inhibition.

—M. O. L.

The hemodynamic action of minimal effective doses of epinephrin in the unanesthetized dog. Dragstedt, C. A., A. H. Wightman and J. W. Huffman, Am. J. Physiol. **84**: 307. 1928.

In 16 unanesthetized dogs adrenalin was injected by vein and blood pressure recorded from a transposed carotid artery. Contrary to the results of previous investigations on anesthetized dogs (and various clinical observations on unanesthetized patients) it was found that the minimal effective dose of epinephrin on sustained administration in the unanesthetized dog produces pressor effects. The minimal effective dose of epinephrin in such animals is less than from 0.2 to 0.4 cc. of a 1 to 1 million solution of adrenalin per kgm. per minute.—R. G. H.

Effect of intramuscular injections of adrenin on the gastrocnemius of a decapsulated frog (Effect de l'injection intramusculaire d'adrénaline sur la contractilité du gastrocnémien de la grenouille surrénalisée). Ferreira, de M., Compt. rend. Soc. de biol. **98**: 467. 1928.

Such injections have little effect. The recuperation of muscles from fatigue which follows injection of adrenin into the dorsal lymph sac is, therefore, due to a central action and not a direct action on the capillaries of the muscle.—J. C. D.

XVIII. The depressor effect of epinephrin in decerebrated animals. Gruber, C. M., Am. J. Physiol. **84**: 345. 1928.

Experiments were made on 8 cats. The animals were decerebrated under ether and adrenalin injected intravenously from ½ to 3 ½ hours later. It was found that epinephrin in small doses caused a fall in blood pressure. Decerebration did not alter the vasomotor response in skeletal muscle. Decerebration heightened the vasoconstrictor action of epinephrin. Epinephrin, when injected intravenously in decerebrated animals frequently caused vasomotor variations to an extent not commonly observed in anesthetized cats.

—R. G. H.

The effect of neurine and ephedrine on the secretion of adrenin (Action de la neurine et de l'éphédrine sur la sécrétion d'adréna-

line). Houssay, B. A. and E. A. Molinelli, Compt. rend. Soc. de biol. **98:** 172. 1928.

Both substances cause a discharge of adrenin but the rise in blood pressure following injection of neurine or ephedrine is not dependent on this discharge. The conclusions are derived from experiments on dogs.—J. C. D.

The size relations of the human adrenal during foetal life (Die Grössenverhaltnisse der Nebennieren im Laufe des Fötallebens des Menschen). Jonsson, E. and N. Aderman, Upsala Läkaref. Förh. **32:** 381. 1927.

One hundred and one normal foetuses from four months to birth, obtained from normal mothers and fixed in formalin, were examined. A steady enlargement of the gland, as shown by tables and graphs, takes place until almost the time of birth. Growth stops then to be continued post-partum.—J. C. D.

The chromaphil tissue and the interrenal bodies of Elasmobranchs and the occurrence of adrenin. Lutz, B. R. and L. C. Wyman, J. Exper. Zool. **47:** 205. 1927.

The two adrenal representatives can be separated without contamination from one to the other in Squalus acanthias, Raja stabuliforis, Raja diaphanes and Raja erinacea. Ringer extracts of interrenals, chromaphil bodies and gastric ganglia were tested by the mydriatic method for the presence of a dilator substance. The interrenals of all four species were negative for a dilator substance and the chromaphil bodies were positive. Extracts of gastric ganglia from Squalus were postive, from Raja diaphanes and Raja erinacea negative, and from Raja stabuliforis sometimes negative and sometimes positive. Extracts of accessory gastric ganglia from Raja stabuliforis were sometimes positive and sometimes negative. All physiological tests were correlated with the presence or absence of chromaphil tissue as seen in sections stained with bichromate. It is concluded that the interrenals of Elasmobranchs do not manufacture or store adrenin. The homology of this gland with the cortical tissue of the adrenal gland of the higher vertebrates leads to the conclusion that cortical tissue does not make adrenin.

—Authors' Abst.

Adrenaline vaso-motor dilation. Macdonald, A. D. and W. Schlapp, J. Physiol. **62:** 12. 1926.

Small doses of adrenaline (0.002 mgm.) may depress the blood pressure of the anaesthetized cat, and various explanations have been given for this phenomenon. It does not appear to have been realized or appreciated that this fall of pressure is very specially

related to the anaesthesia; it is marked under ether and urethane, less marked under chloralose if no ether has been given just before.

In the decerebrate cat from which all traces of ether have been thoroughly ventilated and after the circulation has had time to recover from the effects of anaesthetic, no such depressor response can be evoked, although it was well-marked shortly after decerebration and the level of blood-pressure remains scarcely changed. Depressor doses may now produce prolonged and considerable rises, often interrupted by a notch suggesting a double seat of action of the drug. On ether being supplied to such an animal the depressor response quickly returns. If, as Burn and Dale suggest, adrenaline vaso-dilation be due to the production in the lungs of minute amounts of a histamine-like substance, that substance can only be produced or liberated under the influence of the anaesthetic, for the blood-pressure response to small doses of histamine itself is little affected by the nature or degree of the anaesthetic in an animal with high blood-pressure.—Authors' Abst.

Enlargement of the adrenal cortex in experimental uremia. MacKay, E. M. and L. L. MacKay, J. Exper. Med. **46**: 429. 1927.

After the removal of both kidneys in rats there was an hypertrophy of the adrenal cortex amounting to 45 to 65 per cent. There was no change in the medulla.—M. O. L.

Suprarenal tissue in the food of mice. Effects on the development of the organism and on the sexual function (Le tissu surrenal dans l'alimentation des souris. Effects sur le developpement de l'organisme et sur la fonction sexuelle). de Mira, F., jun., Arch. portug. des sc. biol. **2**: 84. 1927. Abst., Physiol. Absts. **23**: 107.

Feeding suprarenal tissue to mice produces hypertrophy of the testicles, increased muscular activity and pugnacity.

Addison's disease in association with amyloidosis. Philpott, N. W., Ann. Int. Med. **I**: 613. 1928.

Review of 2550 autopsy cases in the University of Michigan Hospital revealed 14 of definite Addison's disease. The associated conditions were tuberculosis, 7; carcinoma metastases, 4; mycosis fungoides, 1; simple atrophy, 1; and amyloidosis, 1. The case of amyloidosis, which is here described, gave a clinical picture of typical Addison's disease. Microscopic examination showed both adrenals almost completely replaced by amyloid, more marked in the medulla and inner portion of the cortex than at the periphery. The semilunar ganglia were involved also. There was a generalized amyloidosis which was thought to be due to an old pulmonary tuberculosis. There was no tuberculosis of the adrenals.—Author's Abst.

Studies on adrenal insufficiency. IV. The influence of intravenous injections of Ringer's solution upon the survival period in adrenalectomized dogs. Rogoff, J. M. and G. N. Stewart, Am. J. Physiol. **84**: 649. 1928.

Marked prolongation of the survival period or the period of good health was caused in adrenalectomized dogs, by daily intravenous injection of Ringer's solution (generally about 100 cc. per kgm. of body weight). Dextrose was almost always added. A table is given showing results on 17 animals. One lived 13 days, 15 hours; one 14 days, 4 hours; one 14 days, 20 hours; one 15 days, 5 hours; one 17 days, 6 hours; one 19 days, 8 hours; one 19 days, 12 hours; one 20 days; one 20 days, 3 hours; one 32 days, 17 hours; one 33 days, 5 hours; one 38 days, 2 hours; one 53 days, 16 hours. Marked amelioration of symptoms, even when acute, was almost always produced during and immediately following injection. Sometimes animals have been rescued, when already comatose, and have lived a long time in good health. Possible ways in which the injections may act are discussed in the paper.—Authors' Abst.

Studies on adrenal insufficiency. V. The influence of adrenal extracts on the survival period of adrenalectomized dogs. Rogoff, J. M. and G. N. Stewart, Am. J. Physiol. **84**: 660. 1928.

Dogs subjected to double adrenalectomy were treated by intravenous administration of extracts of the cortical portion of adrenal glands. The criterion adopted to determine the efficacy of the extracts was the effect on the survival period. In a large series of controls the majority of the animals survived about a week to 10 days, a number less than a week. About 8 per cent survived a fortnight or somewhat longer. Among the animals that were treated with adrenal extracts about 25 per cent survived beyond the upper limit observed in the controls (18 to 78 days). Of those that did not exceed the survival period of control dogs many reached, or nearly reached, the maximum survival period. In these, as well as in the animals that survived longer, there was observed amelioration of symptoms and at autopsy the condition of the alimentary canal was found to be much less severe.—J. M. Rogoff.

Chloralose and the secretion of adrenin (Chloralose et adrénalinosécrétion). Tournade, A. and H. Hermann, Compt. rend. Soc. de biol. **98**: 306. 1928.

When the adrenal vein of one dog (A) is anastamosed to the jugular of another (B) whose adrenals have been removed, effects of adrenin secretion can be measured by injecting substances into A and measuring the blood pressure changes in B. Such experiments show that chloralose stops the secretion of adrenin for a short time.—J. C. D.

Adrenin output in peptone shock (L'adrénalino-sécrétion au cours du choc provoqué par injection intraveineuse de peptone). Tournade, A. and H. Hermann, Compt. rend. Soc. de biol. **98**: 342. 1928.

Experiments using the jugular-adrenal anastamosis method with dogs proved that there was an initial fall followed by a marked rise in adrenin secretion following intravenous injection of peptone.
—J. C. D.

The cholin forming properties of the adrenals (Fonction cholinigène des surrénales). Viale, G., Compt. rend. Soc. de biol. **98**: 177. 1928.

After adrenalectomy there is no diminution of cholin in the blood. The blood of the adrenal vein contains almost twice as much cholin per litre as does the general circulation.—J. C. D.

The supposed antitoxic action of the adrenals (Fonction antitoxique supposee des surrenales). Viale, G., Compt. rend. Soc. de biol. **98**: 178. 1928.

The toxic action of the serum from adrenalectomized dogs, when tested on the heart, is not due to toxins which are normally neutralized by the adrenal, but to toxins absorbed from the intestinal tract as the result of the injuries to the mucous membrane following adrenalectomy.—J. C. D.

The influence of adrenalin and of some other internal secretions on the contractions of skeletal muscle of warm-blooded animals (Ueber den Einfluss des Adrenalins und einiger anderer Inkrete auf die Kontraktionen des Warmblüterskelettmuskels). Wastl, Helene, Arch f. d. ges. Physiol. **219**: 337-390. 1928.

Adrenalin injections tend to inhibit muscle contraction, though the limiting concentration before the effect is shown differs for different animals and is in general higher for males than for females (experiments on the tibialis anterior muscle of cats under urethane). Thyroid produces no direct effect, but the effect of adrenalin after thyroid is lessened (as also after pituitary extracts). Histamine appears to have a direct toxic action on these skeletal muscles.
—A. T. C.

Neuroblastoma of the adrenal in young children. Wollstein, Martha, Surg. Gynec. Obst. **46**: 774-782. 1928.

Of nine sympathicoblastomata of the adrenal medulla in young children, three contained areas of ganglioneuroma in parts of the tumor. One had metastisized very generally to the bones, dura, and liver. Seven were inoperable when first diagnosed. The other two were removed by operation before metastases occurred and both children recovered, one being still alive 17 months after operation, a longer period than any previously recorded.—A. T. C.

Alterations in the homoplastic grafts of endocrine organs (Ricerche intese a modificare il destino dell'innesto omplastico di organi a secrezione interna). Castiglioni, G., Riforma med. **43**: 387-388. 1927.

Starting from the principles that (1) by sensitizing the grafted animal with serum taken from the giver, the grafts are readily reabsorbed and that (2) by blocking the reticulo-endothelial apparatus the grafts held well, and anaphylactic shock was prevented, the author chose the opposite way and tried to "desensitize" the grafted animals. After the grafting, small doses of extract of the homologous organ were injected into the grafted animal every other day, beginning with the second day after operation. The controls were grafted but not treated afterwards. As a result in the treated animals the grafted ovary, for instance, did not begin to degenerate before 100 to 150 days, while in the controls the destruction of the organ was complete after 50 days. Considering that the chosen animals were not either previously or afterwards deprived of the corresponding organs, the author considers these results as very encouraging. He does not attempt any explanation, but advances the hypothesis that the phenomenon may be due to "desensitization."

—G. V.

Endocrinological formulae in children at various age periods (Uber die endokrinologische Formal bei Kindern in verschieden Altersperioden). Fertik, J. M., A. J. Majanz, and S. M. Monossohn, Jahrb. f. Kinderh. **115**: 363. 1927.

This study is based upon autopsy material of 214 cases in which the weight of the thymus, adrenals, thyroid and pituitary was taken. The pancreas and sex glands were not included, as they have external glands as well. While the results are not definitely conclusive and require further study, the authors were able to show that there are five growth periods, corresponding to birth to 7-8 months, 2-6 months, 4½ years, 7-8 years and 14 years. The findings in the adrenals especially require further study as the growth in boys and girls differ so radically that an average cannot be struck. For girls up to 11 years there is a slow growth with but two zones, 6 months and 4 years, remaining high from the latter period up to the 11th year. In boys, five zones of growth are found. The weights of the thyroid and adrenals show a gradual rise from birth up to the 12th or 13th year. This curve has definite periods dividing it into definite zones. The relation in growth between the thyroid and adrenals at certain age periods is quite pronounced, giving the so-called adrenal-thyroid quotient. The periods are those mentioned above. The pituitary and pineal have similar growth periods.—M. B. G.

The purification of heparin and its chemical and physiological reactions. Howell, W. H., Bull. Johns Hopkins Hosp. **42**: 199. 1928.

A method of extraction and purification of crude heparin is described which gives a product free from phosphorus and nitrogen. The reactions of the purified heparin indicate that it is a carbohydrate derived from glycuronic acid. One milligram of this material is sufficient to prevent approximately 100 cc. of blood from clotting for 24 hours or longer. Solutions are stable and may be sterilized by boiling. The material has been used with good results as an anti-coagulant for blood transfusions.—M. O. L.

Diagnosis of pregnancy by detection of hormone in the urine (Schwangerschaftsdiagnose aus dem Harndurch hormonnachweis). Ascheim, S. and B. Zondek, Klin. Wchnschr. **7**: 8. 1928.

Ovarian hormone in the urine does not serve as a biologic diagnosis of pregnancy, as it does not appear in the urine during the first eight or ten weeks. Even later it cannot always be demonstrated with certainty. Besides it occurs in non-pregnant women with functional disorders, especially during the menopause. On the contrary, the determination of the hormone of the anterior pituitary lobe in human urine is of definite value in the diagnosis of pregnancy, especially for early diagnosis. The test is made by injecting 1-2 cm. morning urine into five young mice and the effect upon the ovary established. For control, 4 cm. of urine are injected into an adult castrated mouse. This makes it possible to differentiate between the ovarian and anterior pituitary hormone. An enormous increase of the anterior pituitary hormone in the urine is characteristic of pregnancy. In 16 marked endocrine cases the reaction was slightly positive in three; in two cases of marked myxoedema, and in one case of acromegaly. However, these cases are easily excluded in pregnancy because they are not so prevalent. Cases, especially where there is an increase in the tissue growth, as in pregnancy, were investigated, e. g. carcinoma (22 cases). Reaction was found positive, particularly in carcinoma of the genitals in the female. In round numbers one-fifth of the cases were positive. In 78 cases of pregnancy examined, 76 were positive. The reaction is found positive five days after cessation of menstrual period. The error in these tests amounts to 4 per cent. The technic of the methods will be published in a later article.—H. G. Beck.

Changes in the urogenital apparatus of the female Triton cristatus following testicular grafts (Modifications de l'appareil uro-génital du Triton cristatus femelle après greffe de testicules). Beaumont, J., Compt. rend. Soc. de biol. **98**: 563-564. 1928.

In this urodele the glandular lining of the tract comes to resemble more nearly that of the male, but no new structures corresponding to male organs are formed.—J. C. D.

The female sex hormone (Sur les hormones sexuelles de la femelle). Bencan, C. Champy, and T. Keller, Compt. rend. Soc. de biol. **97**: 229. 1927.

Water extracts from the corpus luteum, when injected into guinea pigs, produce congestion of the uterus and of the mammary glands. A similar effect is given by water extracts of placenta. This is in contrast to the hormone of Allen and Doisy, which is associated with lipoids and found in the follicular fluid and placenta. The changes in menstruation are due to these two hormones acting consecutively, while those of pregnancy are due to their simultaneous action.—J. C. D.

Over-masculinity in the cock. New evidence favoring the theory of a quantitative action of the sex hormone (L'hypermasculinisation chez le coq. Nouvel argument en faveur d'une théorie de l'action quantitative de l'hormone sexuelle). Benoit, J., Compt. rend. Soc. de biol. **98**: 538. 1928.

In partially castrated males the comb, while slower in growing than in controls, finally attained a greater size. This is evidence that removal of a part of the testes has stimulated the remainder to the production of more hormone than normal and that this hormone acts quantitatively and not according to an "all or none" law. —J. C. D.

Pseudo-pregnancy produced by the persistence of a corpus luteum spureum (Pseudo-grosses créée par la persistance d'un corps jaune périodique). Courrier, R., H. Duboucher and E. Pouget, Compt. rend. Soc. de biol. **97**: 271. 1927.

A woman developed the signs of pregnancy, including suppression of menstruation, enlargement of uterus, and morning sickness. After three months, menstruation reappeared. At operation a mass on the right ovary, mistaken for an extra-uterine pregnancy, was found to be a corpus luteum. No signs of implantation were found. This seems to be a true case of pseudo-pregnancy similar to that found in the rodents and dependent on the persistence of a corpus luteum.—J. C. D.

Is the Allen-Doisy test specific for the female sex hormone? Dohrn, M., Klin. Wchnschr. **6**: 359. 1927.

The writer asks this question after a study of animal reactions to injections of extracts of plant material.—E. A.

Inhibition of ovulation by the corpus luteum (Sur l'inhibition de l'ovulation par le corps jaune). Gley, P., Compt. rend. Soc. de biol. **98**: 504. 1928.

The author has developed a method (to be reported) of preparing non-toxic corpus luteum extract. Daily subcutaneous injections

in rats caused a suspension of the oestrous cycle, as followed by the vaginal smear, as long and only as long as such injections were continued.—J. C. D.

Cyclic variations of the sex hormone content of the blood in women (Die Schwankungen des Sexualhormongehaltes im Blute der Frau). Hirsch, H., Arch. f. Gynäk. **133**: 173-185. 1928.

A brief review of the literature is followed by the author's report on 73 blood determinations in women in various stages of the menstrual cycle. This shows that the hormone is not present in appreciable quantities during the early part of the menstrual cycle. It appears first about the middle of the menstrual cycle. The concentration increases until the onset of the flow, when it falls rapidly until it is barely perceptible the following day. The hormone curve corresponds to the growth curve of the endometrium. In pregnancy, the hormone appears about the sixth week and from that time the concentration in the blood increases until the onset of labor. It is more concentrated in menstrual blood than in the puerperium. Thirteen days after childbirth, the circulating blood is negative for the hormone. Lochia gives positive results for at least 27 hours. Elimination of the hormone from the circulating blood occurs through the menstrual flow and lochia. The placenta plays an important role in the production of the hormone in the latter months of pregnancy. Similarity is noted in the development of the corpus luteum and the increase of concentration of the hormone in circulating blood of non-pregnant women.—J. P. Pratt.

Concerning female sex hormone, especially Menformon. Laquer, E., München. med. Wchnschr. **74**: 2045. 1927.

A review of recent work with especial attention to the author's contributions to the subject.—E. A.

The female sexual hormone, menformone. VII. The action of the ovarian hormone, especially menformone, administered by mouth, and the importance of its administration in several doses (Ueber weibliches Sexualhormon, Menformon; über die Wirkung von Ovarialhormon, im besonderen von Menformon per os, und über Bedeutung der Verteilung der Dosis). Laqueur, E., P. C. Hart and S. E. de Jongh, Deutsche med. Wchnschr. **53**: 1583. 1927. Abst., Chem. Absts. **22**: 617.

The dosage of menformone is 100 times as great when given to rats by mouth as when given subcutaneously. In mice, it is only 11 times as great. The same amount of hormone is much more effective when given in several doses than when injected in a single dose.

The influence of the internal secretion of the ovary on the calcium blood level and on calcium metabolism. Mirvish, L. and L. P.

Bossman, Quart. J. Exper. Physiol. **18**: 11. 1927. **The effect of ovarian extracts on the calcium blood level.** Ibid, p. 29.

A method is described for the preparation of ovarian extracts that will produce depression of blood calcium in rabbits, and, in smaller doses, comparable effects in human subjects. The maximum effect occurs in 24 hours, with complete recovery in 48 hours. This effect is suggested as a means of standarizing ovarian extracts. The effect is irrespective of sex.—C. I. R.

The causation of the anoestrous period. Parkes, A. S. and F. W. R. Brambell, J. Physiol. **64**: 388. 1928.

In mice a prolonged environmental temperature of about 0° C. has no permanent effect on the anoestrus period except an initial lengthening of the period; from this it is concluded that the prolonged winter anoestrus of wild rodents is due to diminished food supply rather than to lowered temperature.—C. I. R.

Studies on the internal secretion of the ovary. V The oestrus-inhibiting function of the corpus luteum. Parkes, A. S. and C. W. Bellerby, J. Physiol. **64**: 233. 1927.

A method is described for the preparation of an oestrus-inhibiting extract. The corpus luteum of ovulation is not the organ of oestrin elaboration. Inhibiting of oestrus and ovulation during pregnancy is only one of several functions of the corpus luteum.
—C. I. R.

The cyclical growth of the vesicula seminalis in birds is hormone controlled. Riddle, O., Anat. Rec. 37: 1. 1927.

Two cases were found in feral birds (oven-bird, wood-thrush) of normal enlargement of both (right and left) vesicules seminales, although no sperm was or could ever have been present in one of them. This was because of the absence of a testicle in one case, and the dislocation (mesentery) of a normal testis in the other. This cyclical growth, amounting to at least 2,000 per cent, undoubtedly is based on hormone action, probably on that of the testis. It is pointed out that all of the few known cases of marked cyclical growth, antlers of deer, oviduct and uterus, are also of endocrine origin.—Author's Abst.

The study of the internal secretion of the ovary. The properties of the follicular liquid. 1. Concentration, properties of the folliculine. Simonnet, S., Ann. de Physiol. **3**: 586. 1927. Abst., Chem. Absts. **22**: 449.

The preparation of the hormone is soluble in H_2O and in lipoid solvents. It contains no P or N, but only C, H and O. It is sensitive to oxidation agents, but resists the action of heat, especially in

acid or neutral media. The further study of its properties can only be undertaken after the isolation of the hormone in the pure state.

The importance of the pituitary in the mechanism of development as activator of gonadal secretion (Die entwicklungsmechanische Bedeutung der Hypophysis als Aktivator der Keimdrusseninkretion). Steinach, E. and H. Kun, Med. Klin. **14**: 1928.

The first series of experiments was made on infantile rats, in order to find the causes for the late awakening of the testicular incretion (at the time of puberty). Water extracts of the anterior pituitary lobe prepared from cattle were used. Daily injections were administered, each corresponding to about one-quarter of the fresh anterior lobe substance. After 6 to 12 injections an extreme degree of somatic and psychic precocity in animals 38 to 45 days old was produced. Control animals reach puberty after 95 to 100 days. Further control experiments were made by interrupting the series of injections and demonstrating the consequent cessation of development. After resumption of the injections the development proceeded, which indicates that the observed phenomena are entirely due to the hormone of the anterior lobe. The authors conclude that the delay of the activating impulse from the anterior lobe is the cause for the delay of the testicular incretion and the natural maturity. The second series of experiments was made on eunuchoid male rats, in order to find out whether the role played by the anterior lobe on the endocrine mechanism is finished with the activation of the infantile testicle. The authors found that this is not the case and that the anterior lobe hormone also regulates gonadal incretion in the adult and thus protects the virility during life. The eunuchoid animals were brought to full maturity, as shown by the length and width of the seminal vesicles and the prostate, by spermatogenesis and by fully developed libido and potency. An interruption of the injections caused a relapse of the animals into the former state of eunuchoidism, and a resumption of the treatment brought them again to the height of virility. The ovary shows an analogous dependence. The last series of experiments was made on senile male rats to determine whether a fresh supply of anterior lobe hormone could revivify gonadal incretion. Typical senile rats, 19 to 24 months old, were used. After treatment the seminal vesicles and prostates were found to be considerably enlarged and filled with secretion, the musculature and intestinal tract were hyperemic and the psychic phenomena showed reactivation.—H. Benjamin.

The biological action of the female sex-hormone (Ueber die biologischen Wirkungen des weiblichen Sexualhormons). Steinach, E., M. Dohrn, W. Schoeller, W. Hohlweg and W. Faure, Arch. f. d. ges. Physiol. **219**: 306-324. 1928.

Placental extract of cattle has now been concentrated by a technical process (details of which are not given) to the extent of 50,000

mouse-units per gram, from which preparation the active principle passes into solution to the extent of 500 units per cc. This solution is clear, free from protein, and resistant to acid, alkali, and boiling. It produces no harmful effect on males, even in strongest concentration. Injected into females, it causes marked hyperemia of the mammae through change of tonus in the peripheral vessels. The areola and mamilla of albino guinea-pigs are especially suitable for this test. The mammary apparatus of normal virgin females develops at the about the age of 17 weeks. This development takes place in infantile castrates after three weeks' treatment with the aqueous solution, and the age of 7 weeks. Since the hyperemia is visible after three days' treatment, this biological test can be used quantitatively. The mammary development is marked. Surface and vertical sections of the mammae show the typical close-packed lobules, separated by little fat and fibrous tissue, composed of large hyperplastic acini surrounded by high epithelium, the lumina filled with fat-rich secretion as in normal lactating glands. Secretion into the acini commences during the fourth week of treatment. Milk production, filling the ducts and sinuses, is recognizable after 7 to 8 weeks' treatment. The first period of milk-production lasts from 23 to 25 days, nearly as long as the lactation period of a primipara guinea-pig. The later period, produced through subsequent injections, lasts a shorter time. Complete appearances of hyperplasia and milk-secretion have been observed in females castrated at four weeks, when treatment commenced immediately after castration; in females also castrated at four weeks, when treatment only commenced two months later, and in males castrated at four weeks, who took on marked female characteristics. The uterus of the infantile castrates, especially the uterine mucous membrane, is markedly affected by the treatment, becoming hyperemic, with dilated blood vessels, and the whole organ increases in weight. The microscopic picture shows corresponding changes.—A. T. C.

Follicular liquid and ovarian hormone. Truffi, G., Arch. di sc. biol. **10**: 787. 1927. Abst., Chem. Absts. **22**: 456.

In experiments on the action of small doses of follicular liquid on females, the findings of other investigators were confirmed. Larger doses administered subcutaneously over a period of 20 to 40 days led to the prolongation of oestrus. In sexually developed animals, even though castrated, there appeared the typical genital phenomenon of post-oestrus which is normally observed on the presence of corpus luteum. In the immature animal sexual characteristics were also influenced. Follicular liquid may, therefore, replace the corpus luteum and interstitial glands. Follicular liquid had an "antitesticular" and "antimasculine" action on males. In the guinea pig there was a stoppage of spermatogenesis and a development of the mammary gland, and on the cock there was a change in the rate of

development of the comb. Follicular liquid produces the same genital modifications as are produced in the normal animal by the ovary. The liquid must, therefore, contain the specific ovarian hormone. The hormone shows a physiological and a sexual specificity, but not a species specificity.

A hormone of heart movement. IX. Experiments with a heart-extract of warm blooded animals (Ueber ein Hormon der Herzbewegung. IX. Vorsuche mit einem Herzextrakt vom Warmblüter). Haberlandt, L., Arch. f. d. ges. Physiol. **219**: 279-285. 1928.

Similar results were obtained to those given by extracts from frogs' hearts.—A. T. C.

The origin of the glucose in the hyperglycemia induced by pituitrin. Clark, G. A., J. Physiol. **64**: 324. 1928.

Studies were made on decerebrated, eviscerated cats whose blood sugar concentration was maintained constant by continuous glucose infusion throughout the experiment. Injection of 1 cc. pituitrin caused a fall in blood sugar within one hour. Simultaneous determination of hemoglobin showed that this was not due to blood dilution. Exclusion of the supra-renals from circulation did not alter the response. When pituitrin was followed by insulin injection, the blood sugar decrease by the latter was not retarded. With the liver excluded from circulation blood sugar concentration after insulin fell at about the same rate. It is concluded that the source of glucose in pituitrin hyperglycemia is the liver glycogen.—C. I. R.

Effects of thymus, muscle and pituitary extracts on normal and thyro-parathyroidectomized dogs. Larson, E. and N. F. Fisher, Am. J. Physiol. **84**: 330. 1928.

Experiments were made on 31 dogs from which the thyroids and parathyroids were removed. It was found that extracts of calf thymus and muscle prepared by the same methods used in preparing potent parathyroid extracts have a slight ameliorative action on acute parathyroid tetany. These extracts, as well as pituitary extracts, do not cause sufficient changes in the calcium of the blood to account for their ameliorative action. No parathyroid-like principle could be demonstrated in the extracts as prepared.—R. G. H.

Glandular elements in the posterior lobe of the human hypophysis. Lewis, D. and F. C. Lee, Bull. Johns Hopkins Hosp. **41**: 241. 1927.

Glandular tissue was found in the neural lobe of the human hypophysis cerebri at all ages. The authors studied complete serial sections of 30 human hypophyses and many other individual sections. Tubulo-racemose glands communicating with the hypophyseal cleft were seen frequently in the new-born and in children up to the fourth

year. After that time only occasional tubular glands were seen. The tubular glands were usually situated in the anterior and lateral portions of the posterior lobe, as well as the point of attachment of the hypophyseal stalk. In the gland cells was seen colloid material which stained like the substance found in the duct, cyst or cleft into which the gland emptied. The other chief glandular element was a basophilic cell which resembled the basophile of the anterior lobe in many particulars. This cell was present at all ages, but became more numerous, and invaded the posterior lobe progressively with increasing age. Masses of these basophilic cells were sometimes found high up along the hypophyseal stalk and near the dorsum sellae. Both varieties of these glandular elements were derived from the pars intermedia. The authors include a brief discussion of the relation of these glandular structures to each other and to the physiology of the posterior lobe.—W. J. A.

The presence of pituitrin in the ventricular cerebro-spinal fluid and its absence in the lumbar cerebro-spinal fluid (Présence d'hypophysine dans le liquide cephalorachidien ventriculaire et dans les liquides de ponction occipitale; son absence dans les liquides de ponction lombaire). Mestrezat, W. and V. Caulaert, Arch. internat. de physiol. **28**: 1. 1927.

The presence of the pituitary principle was determined by the action on the isolated uterus of the virgin guinea pig. Ventricular cerebro-spinal fluid was withdrawn from both dogs and horses by puncture between the occiput and the first cervical vertebra. Though the liquid removed by occipital puncture was active, the liquid withdrawn by lumbar puncture was pharmacologically inactive. From their results these investigators feel that, though the hypophysis is usually considered to be a gland of internal secretion, it is of a special type because the blood and lymph vessels absorb the pituitrin after it has been secreted into the cerebro-spinal fluid.—E. L.

Metabolic tests in dystrophia adiposo-genitalis. Nonnenbruch, W., Deutsches Arch. f. klin. Med. **156**: 312. 1927.

Nonnenbruch, in his article on metabolic tests in dystrophia adiposo-genitalis, cites a case of dystrophia adiposo-genitalis and hypophyseal tumor with lowered basal exchange. A pronounced rise in metabolic exchange took place after a meat diet, the maximum occurring after the 4th hour, and not after the 2nd hour, of food assimilation, as claimed by Kestner, Plaut and Schadow, who deem a single analysis after two hours sufficient for the test. He agrees with Durr, Lubin et al. that a series of analyses are necessary for several hours after a meat diet. Furthermore, he indicates that in the case under discussion the specific-dynamic albumin action does not depend upon the anterior pituitary lobe and calls for a series of analyses after a meat diet to estimate the increase of metabolic ex-

change. He again disputes Kestner's theory. The latter considers the lowering of the metabolic exchange by meat diet as important in differential diagnosis between thyrogenous and hypophyseal obesity. Weight is given to the opinion that centers of the midbrain which influence metabolism are in turn influenced by the hypophysis. Biedl differentiates between a pure cerebral form of Fröhlich type and a pure hypophyseal form of Fröhlich syndrome. There are a number of cases in literature which show an inconstancy in the basal exchange. The lowering of the basal exchange is not necessarily a part of the dystrophia adiposo-genitalis syndrome. The basis for this lowering of exchange is not definitely known. The thyroid may play a part, as in endocrine disturbances several glands are involved.

—H. G. Beck.

Sex-determining action of the anterior pituitary on males (Geschlechtsprägende Wirkungen des Hypophysenvorderlappens am Männchen). Voss, H. E. and S. Loewe, Arch. f. d. ges. Physiol. **218**: 604-609. 1928.

A single implantation of less than 0.02 grams of anterior pituitary gland of the sheep suffices to bring a pre-puberal male mouse to puberty. The stimulating action is only on the testis, the growth of the remainder of the genital tract following secondarily to the accelerated ripening of the testis.—A. T. C.

Growth response to anterior hypophyseal extract by the castrated male rat. van Wagenen, Gertrude, Am. J. Physiol. **84**: 468. 1928.

In controlled experiments on 10 castrated rats, it was found that the growth response to anterior pituitary extract was retained.

—R. G. H.

Influence of epinephrine on the carbohydrate metabolism of fasting rats. Cori, C. F. and Gerty T. Cori, Proc. Soc. Exper. Biol. & Med. **25**: 358-361. 1928.

When epinephrine (0.02 mgm. per 100 gm.) was injected subcutaneously into 24-hour fasting rats, the liver glycogen showed a marked increase. whereas the glycogen stores in the rest of the body decreased on an average a little more than the liver glycogen increased. Determinations of the gaseous metabolism revealed that the R. Q. remained at the fasting level (0.715) after the epinephrine injection, whereas the caloric output increased. It is assumed that epinephrine mobilizes muscle glycogen. The lactic acid thus produced enters the blood stream, is carried to the liver and there deposited as glycogen. This explanation is supported by the observation that d-lactic acid, given by mouth, forms glycogen in the liver of rats.—G. T. Cori.

The insulin requirements on various diets. Blatherwick, N. R., W. D. Sansum, Marion Bell and Elsie Hill, J. Metab. Research, **7-8**: 39. 1925-1926.

A man, 57 years of age, having a very severe case of diabetes, was the experimental subject. The plan of the experiment was to keep the protein and calories constant and to vary the carbohydrate content of the diet. The basal diet contained 281 grams carbohydrate, 72 grams protein, 71 grams fat, and a total of 2,051 calories. In three periods on this diet, 143, 151, and 148 units of insulin were required to keep the urine free from gross sugar. When the carbohydrate of the diet was raised from 281 to 412 grams the insulin requirement was only increased to 166 units. The results show that the insulin requirement is not entirely governed by the potential glucose of the food. The requirement for insulin is dependent upon all of the foodstuffs comprising the diet.—Authors' Abst.

The secretion of pancreatic juice—a glycolytic factor in blood (Die Sekretion des Pancreassaftes—ein glykolytischer Faktor im Blute). Boldyreff, E. B., Arch f. d. ges. Physiol. **218**: 553-567. 1928.

The sugar content of normal fasting animal's blood shows periodic variations. It is lower during pancreas secretion than in intervals between this secretion. In absence or inhibition of pancreas secretion, or during removal of the secretion by fistula, the blood sugar is increased. The pancreatic secretion absorbed into the circulation from the small intestine is considered to be one of the chief factors in changing the value of the blood sugar. Blood sugar is higher during active stomach secretion than when the reaction of the stomach is alkaline. Pancreatic juice contains a glycolytic enzyme.
—A. T. C.

The formation of sugar from fatty acids in the depancreatized dog injected with epinephrine. Chaikoff, I. L. and J. J. Weber, J. Biol. Chem. **76**: 813. 1928.

Repeated injections of epinephrine into depancreatized dogs on the third and fourth days after the withdrawal of insulin and food, caused a glycosuria greatly in excess of the amount that could be accounted for as being derived from the glycogen of the liver, from protein and from glycerol. The authors conclude that the extra sugar was derived from fatty acids.—M. O. L.

The influence of the vagus on the islets of Langerhans. III. Further experiments on vagotomy. Clark, G. H., J. Physiol. **64**: 229. 1927.

Section of the right vagus in cats produced an immediate fall in blood sugar concentration. This is not due to stimulation in the act of cutting, to interfere with pulmonary cardiac function nor to cutting off of impulses to the liver or adrenals. It is suggested that the

effect is due to cutting off inhibitory impulses controlling insulin secretion.—C. I. R.

Relations between the internal and external secretions of the pancreas (Relations entre la sécrétion interne et la sécrétion externe du pancréas). Coelho, E. V. and J. C. Oliveira, Compt. rend. Soc. de biol. **98**: 477. 1928.

In fourteen out of twenty human cases it was shown that an augmentation of the external secretion of the pancreas was accompanied by an increase in insulin output.—J. C. D.

The influence on glucose solutions of insulin and of muscle from a normal and a diabetic dog (Action in vitro de l'insuline et des muscles de chiens normaux et diabétiques sur le glucose). Combes, T. J. C., Compt. rend. Soc. de biol. **98**: 174. 1928.

Normal muscle and insulin destroy in time the rotating power of glucose solutions. Muscle from diabetic dogs influences the rotating power very little.—J. C. D.

Studies on crystalline insulin. III. Further observations on the crystallization of insulin and on the nature of the sulphur linkage. The isolation of cystine and tyrosine from hydrolized crystalline insulin. De Vigneaud, V., H. Jensen and O. Wintersteiner, J. Pharmacol. Exper. Therap. **32**: 367. 1928. **IV. The isolation of arginine, histidine and leucine.** Ibid. 387. **V. The distribution of nitrogen in crystalline insulin.** Ibid. 397.

Detailed precautions are given for the preparation of crystalline insulin. Hydrolysis of crystalline insulin gave 15.6 per cent total nitrogen, 12.2 per cent of tyrosine, and 14.2 per cent cystine combined in the form of a dipeptide, 7.6 per cent free cystine. Both cystine and tyrosine are present in the insulin molecule. The presence of arginine, histidine and leucine has also been proven and that of lysine is indicated. The nitrogen distribution in the insulin molecule is reported in detail.—C. I. R.

Insulin and hypercholesterolemia (L'insuline et l'hypercholestérinémie). Fellegi, G., Ann. de med. **22**: 330-344. 1927.

After a review and discussion of the literature with a good bibliography, the author gives the following résumé: Insulin lowers the blood cholesterol if it is elevated, by stimulating the hepatic cells eliminating cholesterol. Insulin also fixes the cholesterol in the fat of the tissues, inhibits cholesterol production by the adrenals and excites the destructive function of the organs responsible for its destruction. Fellegi believes that insulin treatment is indicated, not only in diabetes, but in cholelithiasis, cholecystis and in icterus due to gall stones.—E. L.

Regulation of glycemia in diabetic dogs by transplantation of varying amounts of pancreas (La régulation de la glycémie des chiens diabétiques par des quantités variées de tissu pancréatique transplanté). Gayet, R. and M. Guillaumie, Compt. rend. Soc. de biol. **98**: 584-586. 1928.

Transplanted pancreas without nervous connections brings blood sugar back to normal within a period of a few hours. The larger the graft the more rapid the return to normal.—J. C. D.

Effect of insulin on the blood sugar in nephrectomized dogs (Influence de l'insuline sur le taux du sucre sanguin chez les animax nephrectomisés). Gnoinski, H., Compt. rend. Soc. de biol. **98**: 785-786. 1928.

Insulin reduces the blood sugar as in normal dogs, but its effects are much prolonged.—J. C. D.

Is there a substance producing hyperglycemia in the blood of diabetics (Existe-t-il dans le sang diabétique une substance a action hyperglycémiate)? Hédon, E., Compt. rend. Soc. de biol. **98**: 564-567. 1928.

Blood from a depancreatized dog was treated according to Loewi's technic, i. e. dialyzed and extracted with alcohol. This extract failed to show, as claimed by Loewi, any hyperglycemic action. —J. C. D.

Basal metabolism in experimental pancreatic diabetes (Le quotient respiratoire et le métabolisme de base dans le diabéte pancréatique expérimental). Hédon, L., Arch. Internat. de physiol. **29**: 175-212. 1927.

Eleven dogs were used. In the 15 tables included in the paper the CO_2 exhaled, O_2 consumed, urea and sugar excretion, and heat production are given for the normal animal, after making a pancreatic graft and after removal of the graft. The results show that there is an augmentation of the basal metabolic rate after pancreatectomy. This effect is not due to the trauma of the operation, nor to the removal of the external secretion of the pancreas. This increase becomes greater during the survival period of the animal and usually there is a 30 per cent increase. The cause of this elevation is obscure, but it may be due to increased sugar formation from the proteins.—E. L.

Mechanism of the action of synthalin. Hetenyi, G., Klin. Wchnschr. **6**: 2288. 1927. Abst., Chem. Absts. **22**: 814. 1928.

During the hypoglucemic crisis following an injection of insulin, the glucose concentration in the blood and tissues is markedly reduced; but the total carbohydrate content of the liver is increased.

The author believes that the crisis is brought on by the action of the liver cells. Synthalin, unlike insulin, reduces the carbohydrate content of all of the tissues, including the liver, and a hypoglucemic crisis is not obtained after administration of synthalin.

A study of 22,800 blood sugar estimations—fasting and postprandial —in non-diabetic individuals. John, H. J., Ann. Int. Med. **1**: 470-481. 1928.

The author in the analysis of his data found that 14.14 per cent of the blood sugars were below 80 mgm. per 100 cc. of blood; 7.85 per cent were below 75 mgm., and the lowest value was 30 mgm. This indicates that low blood sugars are not of infrequent occurrence in the normal human being, as none of these patients had registered any complaints. John believes that there should be no alarm when exogenous insulin lowers the blood sugar below 60-65 mgm. because the endogenous insulin apparently does the same.

—E. L.

Ideals in the treatment of diabetes and methods for their realization. Joslin, E. P., New England J. of Med. **198**: 379. 1928.

The effectiveness of the treatment of diabetes is shown in certain striking cases. What can be done for these can be done for most diabetics. High fat diets should be avoided, as they favor arterio-sclerosis and premature old age. Careful diet helped with small amounts of insulin is the best treatment. A camp for diabetic youngsters, where they can enjoy out-of-door sports has proved very successful.—J. C. D.

The hyperglycemic effect of blood from depancreatized dogs (Action hyperglycemiante du sang des chien dépancréaté). Képinov, L. and S. Petit-Dutaillis, Compt. rend. Soc. de biol. **98**: 425. 1928.

If blood from a diabetic dog is injected into a normal dog, the blood sugar rises sharply, sinks to almost normal, and then rises again. If glucose or blood from normal dogs just after a glucose injection is used, there is a rise in blood sugar, followed by prolonged hypoglycemia. The assumption is made that in diabetic blood there is a substance "glycemine," which opposes the fixation of glucose by the cells.—J. C. D.

The sugar content of whole blood of different vessels and its partition between plasma and corpuscles under normal conditions and after insulin and adrenin administration to angiostomised dogs (Vollblutzuckergehalt verschiedener Gefässgebiete und seine Verteilung auf Plasma und Formelemente unter normalen Verhältnissen und bei Insulin—und Adrenalineinverleibung nach Versuchen an angiostomierten Hunden). Kotschneff, Nina, Arch. f. d. ges. Physiol. **219**: 407-410. 1928.

Insulin hypoglycemia is produced through decreased liver sugar-production and relatively increased sugar output to the organs. Adrenin hyperglycemia is brought about especially by increased mobilization from the liver. During absorption from the intestine relatively more sugar is taken up by the corpuscles than during sugar-mobilization from the liver, during fasting or after adrenin injection, and also in hypoglycemia following insulin. During fasting muscles draw equally from plasma and corpuscles, spleen draws from neither, while other organs draw more from plasma than from corpuscles. Under insulin action, the organ tissues not only do not derive sugar from the red cells, but part of the plasma-sugar passes into the corpuscles.—A. T. C.

On the increase in insulin following injection of posterior lobe extract (Sur les causes de l'hyperinsulinémia consécutive a l'injection d'extrait hypophysaire postérieur). LaBarre, J., Compt. rend. Soc. de biol. **98**: 330. 1928.

Experiments were tried on dogs first, with a circulatory anastamosis between two animals, and then with a depancreatized, decapsulated animal into whose carotid-jugular circulation a pancreas was introduced. These showed that posterior pituitary lobe extract increases the insulin in the blood by direct action on the islet tissue, not through vagal action.—J. C. D.

Evidence concerning the effect of insulin on carbohydrate tolerance. LeFevre, W. M., Ann. Int. Med. **1**: 607-612. 1928.

Of the 57 cases of diabetes reported by this author, about half of them required insulin when kept on a Petty diet. Of the patients requiring insulin, 50 per cent were able to cease their injections in two weeks to fourteen months. Some of the cases which still continued insulin were complicated by other conditions. From his results, the author concludes that adult diabetics may improve their tolerance for cabohydrate so that insulin may not be required.

—E. L.

Action of the salts of nickel and cobalt on insulin hyperglycemia (Action des sels de nickel et de cobalt sur l'hypoglycémie insulinique). Magenta, M. A., Compt. rend. Soc. de biol. **98**: 169. 1928.

These salts have no appreciable action.—J. C. D.

Regulations of the blood sugar and water concentrations (Blutzuckerregulation und Wasserhaushalt). Marx, H., Klin. Wchnschr. **6**: 1750. 1927. Abst., Chem Absts. **22**: 624.

A close relationship exists between the blood sugar and water concentrations in the blood. Sugar overeating leads to hyperglucemia and hydremia. Ingestion of water gives a blood dilution curve

that parallels the sugar hyperglucemia curve very closely. The magnitude of the dilution changes induced by ingesting either water or sugar is very largely independent of the absolute quantity of these substances ingested. Repeated ingestion of water or sugar leads to a refractory period. Injection of insulin leads to a hypoglucemia and to a thickening of the blood.

The insulin neutralizing power of the blood of diabetics and non-diabetics (Sur le pouvoir de neutralisation du sang de sujets diabétiques et non diabétiques vis-a-vis de l'insuline). The neutralizing power of the blood for insulin lies in the corpuscles (Le pouvoir de neutralisation du sang vis-a-vis de l'insuline est d'origine globulaire). The neutralization of insulin by the blood is due to an intracorpuscular substance (La neutralisation de l'insuline par les globules sanguins est due a une substance anti-insuline intraglobulaire). Mauriac, P. and E. Aubertin, Compt. rend. Soc. de biol. **98**: 233. 1928.

Defibrinated blood from normals and from diabetics was mixed with insulin. After incubation these solutions were tested for the activity of the insulin by injection into rabbits. In the blood of certain diabetics resistant to insulin treatment, a rapid neutralization of insulin took place. Centrifuging citrated blood proved that this neutralizing power was in the cells By laking the cells it was shown that this was not dependent on their integrity, but was due to an insulin neutralizing substance present in them.—J. C. D.

The effect of successive doses of insulin on the animal body. Ohara, Y., J. Biophysics **2**: 39. 1927. Abst., Chem. Absts. **22**: 266.

After daily injections of convulsive doses of insulin in rabbits, there was an increase in body weight, although convulsions often occurred. A hypertrophy of the cortex of the adrenals was found.

A case of diabetes mellitus that became one of atypical renal glycosuria. Mason, E. H., Canad. M. A. J. **18**: 557-560. 1928.

A woman, aged 68, showed, on admission to hospital, diabetes mellitus, chronic nephritis, chronic myocarditis, hypertension, arteriosclerosis, passive congestion of the lungs and liver, umbilical hernia, and cataract (left). She was balanced with insulin, discharged, and followed through the outdoor department for two months, during which time she was free from glycosuria. Marked failure of compensation appeared, confining her to bed, her appetite failed, and she stopped insulin. She was re-admitted to the hospital eight months after discharge, and again showed glycosuria, but without hyperglycaemia, and gave a typical sugar tolerance curve for renal glycosuria. After 40 days in the hospital (without insulin and with unrestricted carbohydrate) she was discharged, and was admitted 19 days later acutely ill from failure of compensation,

dying 3 hours later. Autopsy showed numerous large islets of Langerhans in the pancreas. The initial diagnosis of diabetes mellitus was based upon a fasting bloodsugar of 0.26 per cent, with glycosuria, and, after control of diet, a moderate fasting hyperglycaemia reacting to insulin, and no glycosuria.—A. T. C.

Treatment of diabetes with an acid-alcohol extract of plants rich in vitamin B. Mills, C. A., Am. J. M. Sc. **175**: 376-383. 1928.

From his clinical experience Mills found that vitamin B stimulated the appetite and growth in children, so extracts of vitamin B rich food were prepared. Alfalfa, sweet clover, corn silk, onions, carrots, etc., were treated with 40 per cent ethyl alcohol containing 0.4 per cent HCl. No heat was used during the process. After extraction, the HCl was neutralized with NaOH and the precipitate removed by filtration. In some cases the alcohol was removed by evaporation. Of the seven cases presented five show that vitamin B decreases the sugar excretion in diabetes. One of the cases was complicated by renal glycosuria and another of the patients left the hospital when the effects were beginning to be definite. The advantage of this extract is that it is effective when given orally.
—E. L.

The insulin-glucose treatment of traumatic shock. Padgett, E. C. and T. G. Orr, Surg. Gynec. Obst. **46**: 783-788. 1928.

The authors consider, from experimental evidence, that probably no better results are obtained by this treatment than by hypertonic glucose or sodium chloride intravenous injections.—A. T. C.

Atrophy of subcutaneous fat following insulin injections. Rabinowitch, I. M., Canad. M. A. J. **18**: 560-561. 1928.

Eight such cases are recorded. In only two were the areas of atrophy of any considerable size. The condition appears to bear no relation to progress. No trace of lipase could be detected in a large amount of insulin preparation similar to that used by these patients.
—A. T. C.

Action of insulin on experimental anaemia in the rabbit. Notes on inhibitory substances in the blood during hyperglycemia (Action de l'insuline sur l'anémie expérimentale du Lapin. Contribution a l'étude des substances inhibitrices du sang, dans l'hyperglycémie). Rentz, E., Compt. rend. Soc. de biol. **98**: 816-818. 1928.

Anemia produced a hyperglycemia. Insulin has less influence on the blood sugar in these cases than in normal animals—J. C. D.

The action of myrtillin in pancreatic insufficiency. Shpiner, L. B., Am. J. Physiol. **84**: 396-400. 1928.

On the basis of experiments on 2 animals it was concluded that myrtillin reduces the hyperglycemia and the glycosuria of a totally depancreatectomized dog (as reported by Wagner and Allen), stabilizing, so to speak, the blood sugar which would otherwise have a tendency to fluctuate within rather wide limits. After the loss of 19/20 of the pancreas, the feeding of myrtillin prevented the development of hyperglycemia and glycosuria. The mild hyperglycemia and glycosuria which followed the administration of desiccated thyroid extract to dogs from which ⅞ of the pancreas had been removed, were eliminated by the administration of myrtillin.—R. G. H.

The action of synthalin on the organism (Uber die Wirkung des Synthalins im Tierorganismus). Simola, P. E., Ztschr. f. physiol. Chemie, **168**: 274. 1927. Abst., Physiol. Absts. **12**: 564.

The lowering of blood sugar after synthalin injection is not so clear and characteristic as with insulin. The lowering is sometimes slight and long delayed, and is in some cases preceded by a marked rise. In some experiments a considerable rise only was observed. When the blood sugar fell, a decrease in the inorganic phosphate was found; in the cases of a rise in blood sugar, the inorganic phosphate also rose. The symptoms of synthalin poisoning resemble those of guanidine poisoning.

Insulin-like substances in higher plants and microörganisms. Simola, P. E., Ann. Acad. Sci. Fennicae **29**: 1927. Abst., Chem Absts. **22**: 1928.

There occurs in plants and bacteria certain substances which can reduce blood sugar considerably. These insulin-like substances are best extracted from the plant material with acid-alcohol or rubbing up the material with picric acid and extracting with acetone. Such substances have been isolated from potatoes, oats hulls, yeast, rhubarb leaves and living and dead bacteria. It was noted in the intravenous and subcutaneous injection of these substances into rabbits that the lowering of the blood sugar (40 per cent in one case) was greatest after 2 hours. One case showed a 4-hour maximum. Actual hypoglucemia convulsions were not observed. Toxic symptoms were produced in rabbits, if the insulin-like substance was not thoroughly purified. On account of the small amount of the pure material available, the chemical nature of these substances could not be determined. Possibly they are guanidine derivatives.

Inflammation involving the islands of Langerhans in diabetes. Stansfield, O. H. and W. Shields, New England J. Med. **199**: 686-687. 1928.

A report is given of the autopsy findings in two girls, one six and one seven years old, who died after acute diabetes.—J. C. D.

The inactivity of insulin injected directly into the intestine and experiments to ascertain the cause of the inactivity (Uber die Unwirksamkeit des direkt in den Darm eingefuhrten Insulins und Versuche zu deren Erklarung). Stasiak, A., Biochem. Ztschr. **188**: 24. 1927.

The work reported was undertaken to ascertain, if possible, why insulin given by mouth has practically no effect on blood sugar. Rabbits were used and the insulin or the control solutions were introduced directly into the intestine through an abdominal window. Eight different series of experiments were carried out, and each series was made up of from 6 to 8 animals. The results reported indicate that insulin dosage of 40 to 80 international units in N/100 HCl directly introduced into the intestine has no blood sugar lowering action; in fact, the blood sugar was in most cases raised. Control experiments with N/100 HCl alone, introduced under the same conditions, gave increased blood sugar, while 9 per cent NaCl was without effect. Rabbits injected with the contents of ligated loops of intestine of rabbits which had been given insulin, 2 to 4 hours previously, again showed no hypoglycemia. Insulin apparently is destroyed or adsorbed by intestinal cells. It was found that insulin incubated with ground intestine at 37 degrees for three hours, with constant shaking, lost its activity. However, if the mixture was not agitated and the insulin was in contact with the intestinal mash for only a short time, it apparently was neither destroyed nor held in a firm union. It could be reactivated quantitatively by alcohol treatment. Intestinal cells previously destroyed by treatment with NaF no longer had the power to inactivate insulin. The last series reported that occasionally a substance can be isolated from the intestine which has insulin-like action. Hypoglycemia and convulsions were produced in starved rabbits injected with a mash of rabbit intestine similar to the insulin experiment, but where insulin was not used.—Estelle Hawley.

Insulin and blood pressure. Strisower, R., Wien. Arch. f. inn. Med. **14**: 429. 1927. Abst., Chem Absts. **22**: 1191. 1928.

A fall in blood pressure and in blood sugar was noted after the injection of insulin in cases of hypertension with diabetes, essential hypertension and hypertension with nephritis. The fall in blood pressure and also in blood sugar was most marked in the diabetics with hypertension, but the fall in blood pressure and in blood sugar did not run parallel. Probably the hormone of the pancreas has a central action analogous to that of pituitrin and of the hormones of other glands of internal secretion, such as the thyroid gland and the hypophysis. The explanation of the fall in blood pressure after insulin is only a part of the problem of hypertension in general.

Insulin and the diabetic pancreas. Susman, W., Edinburgh M. J. **35**: 206. 1928.

This is a study of the islet tissue from thirteen diabetics who had had insulin treatment. Eleven died of coma and two of causes independent of the diabetes. There was more hyperplasia than is found in the islets of untreated diabetics, but evidence of permanent repair was lacking.—J. C. D.

Diabetic coma and insulin (Koma diabeticum und Insulin). Weiss, T., Deutsches Arch. f. klin. Med. **156**: 226. 1927.

A statistical study of the cases of diabetic coma treated in the Dresden-Johannstadt City Hospital from 1910 to 1927 shows that before the use of insulin all patients who entered in a comatose or precomatose condition died; since insulin has been used—a period of about three and a half years—all patients entering in a precomatose condition (15) have recovered, while of the 23 who were in a state of fully developed coma, six have recovered and 17 have died. The seeming discrepancy between the author's results and those of other observers, for instance, of Umber, is explained by the fact that the latter does not distinguish between coma and a precomatose state. Doses of 100-150 units of insulin in the first 24 hours seemed to be more effective than extremely high doses, although no ill effects have been observed from the latter. Intravenous injections of calorose, given usually after the blood sugar has begun to fall, were very effective, but alkali infusions were entirely without effect. In most of the cases of coma in which death occurred, if the patients were not actually moribund upon entrance, the carbohydrate metabolism was controlled by the insulin and death resulted, not from the coma, but from increasing weakness of the heart. In three cases, however, the relapse which followed did not resemble the usual picture of heart failure, but rather that of uremia. The clinical symptoms—increased residual nitrogen, an increased blood pressure after a transient anuria, albumen and clindroids in the urine, the simultaneous appearance of coma and of motor disturbances, all speak for this interpretation, in spite of the fact that at autopsy the kidneys showed almost no pathological changes. The author feels that death probably resulted in these cases from a functional damaging of the kidneys occurring before and during the coma, which was of such severity that the kidneys were unable to recuperate as usual. The picture in these cases therefore parallels that in the cases of heart failure, in which also the anatomical findings do not show sufficient damage to account for death.—H. J. J.

Regulation of metabolism. X. Glycogen in fatty tissue and the possibility of change of fat into carbohydrate (Stoffwechselregulationen. X. Ueber Glykogen im Fettgewebe und über die Moglichkeit der Umwandlung von Fett in Kohlehydrat). Wertheimer, E., Arch. f. d. ges. Physiol. **219**: 190-201. 1928.

After prolonged hunger, followed by food, glycogen (up to 2 per cent) is invariably found in the fatty tissues of rats. In Octo-

ber and November glycogen is invariably found in the fat-bodies of **Rana esculenta,** which remains there during hunger and after strychnine poisoning. The results are considered to support the change of fat to carbohydrate.—A. T. C.

The treatment of parathyroidectomized dogs with cod liver oil. Brougher, J. C., Am. J. Physiol. **84:** 583. 1928.

A controlled study was made on 18 dogs. It was found that addition of cod liver oil to a mixed stock diet for thyro-parathyroidectomized dogs delayed the onset of tetany and lessened its severity when it did occur. Serum calcium in control and in test animals dropped to the tetanic level, but tended to approximate the normal in 30 to 40 days in the animals given cod liver oil. The point is further confirmed that low serum calcium is not always accompanied by tetany. Cod liver oil relieves tetany and benefits parathyroidectomized dogs either by improving calcium absorption, mobolizing body calcium, or increasing the ratio of ionized to un-ionized calcium. Thyro-parathyroidectomized animals have been carried through estrus, pregnancy and lactation by the addition of cod liver oil to the stock diet.—Author's Abst.

Experimental obstructive jaundice. II. Modification of the parathyroid tetany mechanism in jaundice. Buchbinder, W. C. and Ruth Kern, Arch. Int. Med. **41:** 754-763. 1928.

There is a marked diminution generally or an absence of tetany following thyroparathyroidectomy on jaundiced adult dogs and puppies. The survival period after thyroparathyroidectomy is prolonged especially for animals that have been jaundiced for some time. The acutely jaundiced dog is more susceptible to a severe and terminal tetany. Indirect evidence is presented of a functionally or structurally altered mechanism of tetany in obstructive jaundice. This is threefold and is based on: (a) the response of the thyroparathyroidectomized animal; (b) the relief of tetany by the intravenous injection of bile, and (c) the absence of tetany in late obstructive jaundice in puppies in which the blood serum calcium may reach the tetany level.—Authors' Abst.

Calcium content of maternal and foetal blood serum following injection of parathyroid extract in foetuses in utero. Hoskins, F. M. and F. F. Snyder, Proc. Soc. Exper. Biol. & Med. **25:** 264. 1928.

In these experiments in which parathyroid extract (Collip) was injected into foetuses in the dog, there was no evidence that the active substance reached the maternal circulation, as indicated by the calcium content of the maternal blood serum. The foetal blood serum obtained at the end of each experiment was found in the non-injected foetuses to be about 1 to 3 mgm. higher in calcium than

the maternal serum. In foetuses which had been injected previously with parathyroid substance, the calcium content of the serum was more than 3 mgm. higher than in the maternal serum. These findings in the case of parathyroid extract are in agreement with previous observations which have been made upon the effect on the mother of the injection of insulin, adrenalin, and pituitrin in rabbit and guinea pig foetuses, in utero. No evidence has been obtained that these endocrine substances pass from foetus to mother across the placental boundary.—M. O. L.

Parathyroid extract as a factor in ossification and growth. Ortega, F. E., Progresos de la clínica **35**: 836. 1927. Abst., J. A. M. A. **90**: 653.

Experiments on dogs and clinical tests in three little girls demonstrated that the parathyroid hormone is apparently an important agent in bone and body growth. This is the treatment of choice in any case of retarded growth in which thyroid medication has brought the basal metabolism to normal, but has left the growth disturbance uncorrected. Doses of parathyroid extract should be very small and should be associated with oral administration of calcium lactate.

The effect of parathyroid extract on mineral metabolism in infantile tetany. Shohl, A. T., A. M. Wakeman and E. Y. Shorr, Am. J. Dis. Child. **35**: 392-397. 1928.

Small amounts of parathyroid extract were administered to two patients with infantile tetany. It had little effect on one child, while in the second it controlled the symptoms and showed an improvement as measured by clinical and chemical results. The improvement was transitory and ceased when treatment was discontinued. The alteration in the chemical picture was brought about without gross change in either calcium or phosphorus metabolism. During the period of administration of the parathyroid extract (with relief of symptoms) there was a normal excretion of sodium and potassium. During the relapse following withdrawal of the extract, the excretion of sodium was increased and potassium was retained.—M. B. G.

Tetany and chronic diarrhea. Snell, A. M. and H. C. Habein, Ann. Int. Med. **1**: 694-706. 1928.

A case of tetany in which diarrhea was the undoubted cause is reported. The tetany was controlled by the administration of parathormone and calcium lactate. A discussion of the relation of tetany to the gastro-intestinal tract is included.—E. L.

Influence of thyroidectomy on the absorption of water by the tissues (Action de la thyroidectomie sur l'hydrophilie tissulaire). Bernardbeig, J. and M. Sendrail, Compt. rend. Soc. de biol. **98**: 578-580. 1928.

Thyroidectomized rabbits were tested for the rate of water absorption by subcutaneous injections in the lobe of the ear. In three out of five which showed typical symptoms of hypothyroidism, absorption was more rapid.—J. C. D.

Hyperthyroidism caused by pyelitis. Bonilla, E. and J. F. Velasco, Med. ibera **1**: 201. 1928. Abst., J. A. M. A. **90**: 1672.

In a girl, aged 23, a typical hyperthyroid synodrome-goiter, tremor, tachycardia, loss of weight—followed pyelitis of calculous origin. The condition subsided completely after the pyelitis was cured. Previous antithyrois treatment had failed.

Creatine excretion in artificial hyperthyroidism. Carson, D. A., Proc. Soc. Exper. Biol. & Med. **25**: 382. 1928.

Following a recent report on the excretion of creatine in hyperthyroidism and the effect of iodine therapy upon this condition, an attempt was made to produce creatinuria experimentally by the administration of thyroid extract. Three subjects were used, two of whom were in good health, and one an elderly man suffering from arteriosclerosis. Large amounts of thyroid extract were required to elevate the basal metabolism and produce creatinuria and the excretion was irregular except in the case of the arteriosclerotic individual. His excretion reached a maximum of 483 mgm. The effect of iodine in his case could not be determined.—Author's Abst.

Stammering produced by thyroid medication. Gordon, M. B., Am. J. M. Sc. **175**: 360. 1928.

The untoward symptoms produced by thyroid medication are essentially those of an acute thyroiditis and are generallly disturbances of the central nervous, gastro-intestinal and cardiovascular systems. Stammering may be produced by thyroid extract and should be considered as a manifestation of a general nervous excitation following disturbance of the central nervous system. When observed during the course of thyroid treatment it should be treated as any other toxic symptom by an immediate suspension of the medication. The administration of the thyroid should not be resumed until some time has elapsed after the disappearance of the stammering and then only with small doses. Five cases of childhood myxedema and hypothyroidism are reported in which stammering occurred during the course of thyroid treatment. The relationship between the stammering and the medication is clearly apparent.—Author's Abst.

Histological study of the thyroid of the guinea pig in experimental scurvy. Harris, Katharine D. and Erma A. Smith, Am. J. Physiol. **84**: 599. 1928.

As a result of scurvy (8 cases) the thyroid gland of guinea pigs showed an increased amount of interfollicular cells, a decrease in colloid, an increase in the number of vacuoles, and a lengthening of the cells lining the follicles, the degree of change depending on the length of time the animals survived the scurvy-producing diet. Acute starvation of guinea pigs (2 cases) revealed no changes in the thyroid. The results are interpreted as an indication of involvement of the thyroid as a consequence of vitamin C deficiency.

—R. G. H.

Cataract and postoperative tetany. Jaques, L., Am. J. M. Sc. **175**: 185. 1928.

A good review of cataract formation after thyroidectomy is given by the author, with a history of two cases. Neither of these developed severe tetany, because of being controlled by parathormone medication. The author stresses the point that the postoperative tetany should be promptly controlled, so as to avoid lenticular opacities.—E. L.

Action of thyroxin on the autonomic nervous system (Action de la thyroxine sur l'innervation autonome). Kalnins, V., Compt. rend. Soc. de biol. **98**: 800-802. 1928.

Thyroxin re-enforces the effects of adrenin on the rabbit's intestine and uterus. It seems to increase the excitability of the sympathetic end organs but only in massive doses. In small doses it increases para-sympathetic excitability in the intestine but in large doses paralyzes it.—J. C. D.

The effect of thyroxin on the autonomic excitability of the heart (Action de la thyroxine sur l'excitabilité autonome du coeur). Kalnins, V., Compt. rend. Soc. de biol. **98**: 802-804. 1928.

No influence of thyroxin on the frog's heart could be noted.

—J. C. D.

The influence of the thyroid on the distribution of iodine, sugar and amino acids in the blood (Ueber der Einfluss der Schildrusse auf die Verteilunge von Jod, Glucose and Amino sauren in Blute). Kraft, R., Mittz. Grengzb. Md. u. Chir. **40**: 433. 1927. Abst., Chem. Absts. **22**: 450.

The distribution of the iodide between plasma and the corpuscles is approximately the same where different coagulants are used. It is independent of the amount of iodide and is about the same for different animals of the same species. It is influenced by the proportions of blood cells to plasma. The relationship is not changed by hyperthyroidism or thyroidectomy, but is changed after intravenous injections corresponding with the escape to the tissues.

The distribution of glycine and glucose on the plasma and the corpuscles is the same in normal, hyperthyroid and thyroidectomized animals.

Studies on vigor. XV. The effect of thyroidectomy on spontaneous activity in the rat, with a consideration of the relations of the basal metabolism to spontaneous activity. Lee, M. O. and E. F. Van Buskirk, Am. J. Physiol. **84**: 321. 1928.

The effect of thyroidectomy on spontaneous activity was studied in 18 adult albino rats over a period of three months. The average daily activity after the removal of the glands was essentially the same as before. No objective evidence of lethargy was obtained, although the rats were in a definitely hypothyroid condition. Data from a number of other sources are considered bearing on the question of a possible relationship between the basal metabolic level and the amount of spontaneous activity shown by the animal. In 6 young adult female rats the feeding of thyroid gland substance caused a slight decrease in spontaneous activity. During the oestrual cycle the changes in basal metabolic rate do not correspond with the changes in the activity level. Castration or spaying greatly decreases the activity, but decreases the basal metabolism comparatively slightly. The evidence is entirely against any idea that the amount of spontaneous activity manifested by an animal is dependent upon the basal metabolic level. Neither does the basal metabolic level show any close variation with the amount of spontaneous activity manifested.—M. O. L.

The occurrence of a raised basal metabolic rate in new growth without hyperthyroidism. Mason, E. H., Canad. M. A. J. **18**: 681-682. 1928.

A patient with melano-sarcoma with extensive involvement of the liver had a consistently elevated basal metabolic rate of over plus 40%. There was no evidence of any thyroid disorder and no reaction to Lugol's solution.—A. T. C.

Clinical and pathological evidence of the influence of iodine in the therapy of primary hyperthyroidism. Menne, F. R., T. M. Joyce and J. D. Stewart, Ann. Int. Med. **1**: 912-934. 1928.

A paper containing a history of the relation of iodine to the thyroid gland, advances in the medication of thyroid dysfunction and an analysis of 131 cases of primary hyperthyroidism. Four plates showing the effect of iodine administration on the thyroid gland are included. Though the ages of these cases varied (15-69 years), there were no differences in the clinical and pathological manifestations in these individuals. The prophylactic use of iodine has reduced the severity of the clinical symptoms. Iodine therapy

preoperatively increases the amount of colloid present in the thyroid gland. This accumulation of colloid probably inhibits the secretory function of the thyroid, which accounts for the beneficial effects of iodine preoperatively. The authors believe that the sudanophilic substance is concerned in hormone production.—E. L.

A case of exophthalmic goitre complicated with toxic adenoma treated by lead ionization. Miller, J., P. M. Macdonnell and A. F. G. Cadenhead, Canad. M. A. J. **18**: 400-403. 1928.

Lead ionization accompanied by other treatment produced a marked diminution in the size of the gland and an improvement in the patient's general condition. Owing to the state of the heart surgical treatment was not considered feasible. From the postmortem findings, notably from the degenerative changes found in the main portions of the thyroid, and from the relatively large amounts of lead (3 to 4 mgm.) it contained it is concluded that lead ionization was an important factor in the diminution in size of the thyroid. The foetal adenoma was easily separated and analyzed separately for lead; no trace was found.—A. T. C.

Influence of thyroid and insulin on the oxidases of the various organs. Mori, K., Folia endocrinol. Japonica. **2**: 40-41, 122. 1927. Abst., Chem. Absts. **22**: 460.

The oxidase content of the organs of the normal rabbit, especially of heart and kidney, is increased by insulin injections. A further increase is caused by the simultaneous injection of glucose. Thyroxin has the same effect on heart and kidney. The increase following the simultaneous insulin-thyroxin injection exceeds that produced by each hormone alone. The loss in oxidases caused by thyroidectomy may be made up by injecting insulin.

Action of thyroxin. Schoeller, W. and M. Gehrke, Klin. Wchnschr. **6**: 1938. 1928. Abst., Chem. Absts. **22**: 813.

Thyroxin produces only half the elevation in metabolic rate in castrated males as in non-castrated animals. A similar effect is not obtained in females. The normal female mouse is less reactive to thyroxin than is the normal male mouse.

Nodular goiter with hyperthyroidism. Thomas, H. M., Jr., Arch. Surg. **16**: 117. 1928.

An analysis is presented of 32 cases of nodular goiter with hyperthyroidism in which exophthalmos was not present. The average basal metabolic rate was 38 per cent above normal. From his study the author concludes that all of these cases are instances of hyperthyroidism of a varying degree. Sections from the glands of

each case showed areas of hypertrophy and hyperplasia of the thyroid epithelium. The author divides the cases for study into two groups: patients less than 45 years of age, of which there were 13, and those of 45 years or more, of which there were 19. The glands from 11 of the 13 younger patients presented hypertrophy and hyperplasia of the thyroid epithelium of the variety seen in exophthalmic goiter; in the other two cases of this group the diagnosis of hyperthyroidism was questionable.

In the older group (45 years or older) of 19 patients more or less slight degrees of hypertrophy and hyperplasia of the thyroid epithelium were found in each case. The author believes from a study of these cases that a slight degree of hyperthyroidism, when combined with other morbid conditions, may be sufficient to produce the clinical syndrome. Of this older group 11 patients suffered from heart disease, of whom 9 showed myocardial insufficiency and 8 of these also auricular fibrillation. Of the other 8 patients in this older group one showed primary hypertension (blood pressure 200/100), one showed an anemia of severe degree (hb. 55 per cent), two were obese and one, besides being obese, suffered from arteriosclerosis and hypertension (blood pressure 210/100). It is the author's belief that these factors, coupled with the advancing age of the patient, produce an individual who is more sensitive to slight degrees of hyperthyroidism and that these mild cases of hyperthyroidism (as estimated from the degree of hypertrophy and hyperplasia of the thyroid epithelium) become clinical entities only when coupled with some other morbid conditions. Where other morbid conditions were absent, namely, in the younger group, the degree of hypertrophy and hyperplasia of the thyroid epithelium equaled that seen in Graves disease.

The author concludes that these cases of nodular goiter with hyperthyroidism seem to differ from cases of exophthalmic goiter chiefly in the degree of thyrotoxicosis and occur mainly in elderly persons who are suffering also from other conditions which disturb their circulatory mechanisms.—Author's Abst.